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THE CHICAGO MEDICAL SCHOOL

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AMEBIASIS, A PROBLEM

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Introduction

Kartulis[1] was among the first investigators to recognize the relationship between the human parasite now known as *Endamoeba histolytica* and the disease, amebic dysentery. Since his original reports, the whole disease picture produced by this organism has been extensively investigated by many clinical and laboratory workers, and a great body of information is now available. It is known that the disease-producing potentialities of *Endamoeba histolytica* are not limited to the acute and severe condition with which Kartulis was evidently dealing, but that in many instances infection with this organism results in the development of a chronic disease with varied and irregular manifestations which make diagnosis a problem. Craig[2], in an attempt to simplify diagnosis, classified infections with *Endamoeba histolytica* into four categories with respect to severity and symptomatology of the disease. These ranged from an asymptomatic infection to the severe amebic dysentery.

The Clinical Problem

The clinical diagnosis of amebiasis presents a number of problems, especially within the group of individuals with chronic infections. The clinical signs in this condition are many and varied and include gastro-intestinal distress, flatulence, recurrent diarrhea, joint pains, headache, urticaria, and fatigue. These and certain other symptoms are present to varying degrees in many other conditions and a definite diagnosis of amebiasis cannot, at present, be established without demonstrating the causative agent, *Endamoeba histolytica,* either in stools or in material collected at proctoscopy. The search for *E. histolytica* in stools is time consuming and the final identification of the organism is not easy. Even with satisfactory laboratory conditions, it has been shown that it is necessary to do at least six separate stool examinations, twenty-four to forty-eight hours apart before a reasonably dependable report can be made[3]. Methods for culturing the organism from stool samples or proctoscopic specimens as presently employed leave much to be desired and do not improve greatly on the results of direct search for *E. histolytica.* Complement fixation has been tried as an aid in diagnosis, but the difficulties encountered in producing a satisfactory antigen have hampered the development of this technique. Even with a good antigen this test is difficult for routine laboratory use and it is to be doubted that it offers the ultimate solution to the problem.

Since amebiasis is a protean disease, an additional clinical problem arises after *E. histolytica* has been found and identified in a patient, since it then becomes necessary to decide whether this infection is responsible for all of the observed symptoms.

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In the discussion that is to follow, some of the problems of diagnosis and treatment in amebiasis will be summarized, and a brief description of the approach of research toward the solution of these problems will be given. The points to be made will apply more specifically to the chronic form of the disease as opposed to acute amebic dysentery.

The improvement of methods for the diagnosis of amebiasis is closely associated with the development of knowledge of the nature and habits of the parasite. Little is known of the fundamental growth requirements, strain variation, antigenicity, and pathogenicity of *E. histolytica*. Strain variation, antigenicity, and pathogenicity are particularly important in developing a fundamental understanding of the disease and in studies designed to develop methods of diagnosis. The difficulties which have been encountered in the cultivation of the organisms *in vitro* have made this method unsatisfactory for elucidating the needed information.

Culture Technique

E. histolytica was first successfully cultured *in vitro* by Boeck and Drbohlav[4] in 1925. Their medium consisted of a coagulated egg slant overlaid with Locke's solution, into which they inoculated fecal material from patients with amebiasis. Although *E. histolytica* propagated quite well in their medium, there also developed a large number of bacteria and it was soon discovered that the amebae would not propagate if separated from these other micro-organisms. Thus, the critical problem since 1925 has been that of obtaining active propagation of the amebae in pure culture, or, at least in a state free enough from bacteria to allow the type of careful study which has resulted in the great advances in the understanding of many other infectious diseases. Although numerous modifications of the Boeck-Drbohlav method have been tried, no completely satisfactory routine culture medium is presently available.

The very intimate association between *E. histolytica* and bacteria that exists *in vitro* has, with other things, led to the development of a feeling that the pathogenesis of the parasite may be affected and modified by, or may even completely depend on, the bacterial flora of the intestine of man. A further observation which has somewhat strengthened this feeling is that in the treatment of patients with antibiotics which have a marked effect on the intestinal bacterial flora but do not affect *E. histolytica*, there results a temporary alleviation of symptoms. The nature of some of the lesions produced in the intestine of infected individuals is of some interest. One of the typical lesions appears to result from an invasion by the amebae through the mucosa and then into the underlying tissue. This process results in a flask-shaped ulcer with but a very small opening through the mucosa. Stained sections of the lesions often reveal *E. histolytica* trophozoites which appear to be invading essentially normal tissue at the base of the ulcer. Behind them occurs the necrosis and sloughing of the tissue cells. There is little, if any, inflammatory response and little evidence of cellular lysis in the area immediately surrounding some of the amebae. This might suggest that the amebae are merely opening the way for invasion by bacteria that are normally inhabitants of the intestinal tract. It is also possible that the presence of certain bacteria is necessary for entry of *E. histolytica* into the tissues. However, all the evidence for a combined amebic-bacterial pathogenesis must be regarded as circumstantial, and the final decision awaits further critical experiments. It may be pointed out that the occurrence of amebic liver and brain abcesses which are frequently free of bacteria at first sight might indicate that bacteria are unnecessary. However, it is difficult, if not impossible, to prove that bacteria were not present at the inception of such lesions. Elucidation of the true relationship between *E. histolytica* and certain bacteria may have a great effect on the approach to diagnosis and particularly to the treatment of the disease.

Incidence of Infection

Estimates of the number of individuals in the general population infected with *E. histolytica* vary greatly, and considerable confusion exists on this question. The reasons for this variation and the resulting confusion become apparent when it is realized that the methods of establishing a final diagnosis are not easily applied in routine laboratories and, when applied, require considerable control over the patient. This is particularly true in temperate zones where the preponderance of infections appear to be of the chronic type. The variation in the clinical findings by different investigators in different patients and results of stool examinations reported by different laboratories have, among other things, led to postulations that two or more "types" or "races" of *E. histolytica* exist, some pathogenic and some non-pathogenic. There is no conclusive evidence that this is true, and until definite proof of the occurrence of pathogenic and non-pathogenic "races" is at hand, it would seem that all must be considered potentially pathogenic. It is only reasonable to assume that some strain differences in *E. histolytica* occur in the same manner as in species of bacteria. There is good evidence presented by competent investigators that small and large "races" do exist, but proof of lack of pathogenicity in any group is not conclusive. It has been concluded by some that small race strains are non-pathogenic. Frye and Meleney[5] and others have obtained evidence in animal experiments that differences in the degree of pathogenicity exist between strains of *E. histolytica* isolated from different patients and from different geographical locations. Small race strains were found to be pathogenic in these experiments[6]. In general, strains isolated during outbreaks of acute amebic dysentery were more pathogenic for kittens than were those isolated from persons in areas where chronic amebiasis existed in the population. This is valuable information, but does not give the answer to the critical question as to the nature of the difference. This answer may be in terms of fundamental differences in the amebae, in the nature of the bacterial associates, in the amount of previous exposure of the population to *E. histolytica*, in individual susceptibility of the host, or in any one of a number of other possibilities.

Treatment

The treatment of the patient with amebiasis, once the diagnosis has been established, also presents certain problems. No completely satisfactory drug is yet available, although a number are in use. Emetine has been extensively used, but has serious limitations. Some of the antimalarials (atabrine, chloroquine) have been used with some success, especially in treating hepatic amebiasis, and some of the antibiotics (Aureomycin, Terramycin, neomycin) have shown considerable promise. Still better results have been obtained by some workers using combinations of drugs, such as Aureomycin and chloroquine or Terramycin and chloroquine. More recently, fumagillin has been used with varying results. No drug so far developed, however, appears to be completely adequate. Here again, one of the biggest stumbling blocks in the development of adequate treatment methods and a really effective drug is lack of understanding of the cultural and pathogenic properties of the causative agent, *E. histolytica*. The nature of the media for cultivation of *E. histolytica* has made interpretation of *in vitro* results on testing of amebicides difficult since it cannot be determined with certainty whether a drug is primarily affecting the amebae or the bacterial flora on which the amebae depend. The interpretation of *in vivo* results obtained using susceptible animals (guinea pigs, rabbits, rats, dogs, and kittens) is also difficult for somewhat similar reasons. Evaluation of a drug in humans also presents serious problems. These problems arise from the points discussed previously regarding diagnosis. It is generally agreed that alleviation of symptoms is not a dependable criterion for successful treatment. Thus, it is necessary to base treatment success or failure on the presence or absence of *E. histolytica* in stools. Alleviation of

symptoms is not useless as a criterion; it is merely not conclusive and must be placed in its proper postition. The examination of adequate number of stools depends on considerable control over the patient to assure collection of sufficient specimens over a period of three, six, or nine months. Except in certain institutions, it is a problem to follow a significant number of patients for this period of time.

The Experimental Problem

With this confused and somewhat discouraging picture in mind, it seemed likely to the author a number of years ago that a good point of attack lay in extensive investigations on *E. histolytica* itself. Experiments should be designed to (a) develop media in which the parasite could be propagated in pure culture, (b) study strain variations in *E. histolytica* culturally, antigenically, and pathogenically, (c) ascertain the true relationship between the amebae and the various bacterial associates both *in vitro* and *in vivo*, and (d) having at hand large numbers of the organisms free or almost free of bacteria, investigate the possibilities of developing new diagnostic tools of a simple and usable nature.

Certain progress has been made in the development of means of culturing *E. histolytica* in large number relatively free of bacteria, but no medium is yet available for pure culture studies. However, it is now hoped that sufficient progress has been made to justify attempting to develop new diagnostic aids. Methods have also been developed which, it is hoped, will lead to a better understanding of the pathogenicity of the parasites. Rather detailed accounts of the experiments that have been done have been published elsewhere[7, 8], and only a brief resume will be given here as it pertains to the practical outcome that is hoped to be gained.

Two new media have been developed; one of them yields sufficient harvests of *E. histolytica* trophozoites to allow for studies relative to the development of new diagnostic tools; the other one may be useful in studies of the nature of the pathogenicity of the organism.

Bacterial Substrate Medium

The first medium depends, as do other *E. histolytica* substrates, on a bacterial culture[7]. However, it has the important and fundamental difference that the bacterial cells are not themselves propagating during the propagation of the amebae. Quite to the contrary, the bacterial cells in this medium are undergoing logarithmic death under the influence of penicillin and at the time when the amebae reach their maximum numbers, the bacterial cells are almost all destroyed. It is thus possible to obtain concentrated suspensions of *E. histolytica* trophozoites to use for various studies especially in the direction of improved diagnostic aids. Other studies of fundamental interest will involve attempts at antigenic analysis and metabolic and other studies designed to elucidate the extent and type of strain variations that occur in *E. histolytica.* Although this medium has been used for isolation of *E. histolytica* from the stools of patients, its complex preparation indicates that it could not be used in routine laboratories to replace present cultural methods in the diagnosis of amebiasis.

Tissue Culture Medium

The second medium offers quite different possibilities. It represents the first substrate in which *E. histolytica* propagates without accompanying bacteria or other micro-organisms. This medium is a tissue culture preparation of the Maitland type[9] which utilizes a ten per cent suspension of chick embryo tissues. It is prepared by grinding chick embryos in a mortar without abrasive and making a ten per cent suspension in tissue culture nutrient fluid. Inoculation of these cultures with *E. histolytica* results in excellent propagation of the amebae. A further observation is made when one uses blocks of tissue such as liver lobes or heart instead of, or in addition to, macerated tissues. In these cases the amebae enter the blocks and can be seen lying among the tissue cells when examined in stained sections.

These tissue-bearing cultures now appear to offer several lines of approach to a better understanding of *E. histolytica.*

For the first time there is a chance that we can start with bacteria-free amebae and study their effects on various types of tissues without the influence of the bacteria. With the chick embryo tissues now being employed, the entry of the amebae into the blocks has shown no evidence of any real damage to the tissue cells. This would appear to be a critical observation and when extended to include other types of tissues (animal, human, etc.), this should provide more valuable information. It should now be possible to begin to reconstruct the situation that occurs in the natural infection with *E. histolytica* by adding selected bacteria or bacterial extracts to study their effects on the amebae-tissue complex. Such information may give the key to the real nature of the pathogenesis of *E. histolytica.*

E. histolytica cultures in the tissue-bearing substrate appear to offer chances for evaluation of potential amebicides as indicated by preliminary experiments. The medium presents a substrate in which the amebae propagate in the presence of tissue cells, a situation approaching to a certain extent that which exists in natural infections. It may be argued that, since the amebae depend on the tissues, a drug having primary effects on tissues may only appear to have amebicidal activity. This objection may not be too serious, since a drug having considerable effect on tissues might well be quite toxic in *in vivo* use and would, thus, not be desirable. There are methods by which it can be determined whether or not the drug is having marked effects on the tissues.

It may be of interest here to briefly summarize some of the observations made to date using the two media mentioned above that have bearing on the nature of the growth requirements and strain variations of *E. histolytica.*

Observations on Growth Requirements

Studies have been made on the growth characteristics of several strains of *E. histolytica* in each of the two media, and considerable differences in the growth curves have been noted. These differences are not consistent between the two media; some strains propagate better in the tissue-bearing substrate and others do better in the bacterial substrate.[8,10]

The pH requirements of *E. histolytica* appear to be determined in large measure by the substrate rather than by exacting requirements of the amebae themselves. Thus, all cultures tested propagate best at pH 6.0 in the bacterial medium, but in the tissue substrate the optimal pH appears to be 7.2 to 7.6.[8,10]

Exclusion of oxygen from *E. histolytica* cultures is essential, thus they are classed as anaerobic. The requirements for peptone and carbohydrates appear to be rather exacting on a qualitative basis.

Evidence is quite conclusive that the bacterial cell is the most important contributor to the propagation of *E. histolytica* in the bacterial medium. This represents a real advance in understand the growth requirements of the amebae, since it was previously thought likely that the bacteria were providing some soluble by-product of their metabolism which the amebae needed.

In the case of the tissue-bearing substrate, freshly made tissue suspensions have proven to be necessary for successful propagation of *E. histolytica.* If the substrate is incubated twenty-four hours before inoculation with amebae, propagation is very poor. Thoroughly ground tissue suspensions containing no intact cells fail completely in support of the propagation of *E. histolytica.*

It is of interest here to speculate on the meaning of the observation that the propagation of *E. histolytica* is dependent on the presence of bacterial or tissue cells. At least two possibilities may be considered. First, it is possible that some constituent of the tissue or bacterial cells is essential. This could be an enzyme, nucleic acid, nucleoprotein, or other actual chemical substance. If such were the explanation, one would expect to observe ingested tissue cells or cell fragments in the amebae in the tissue culture substrate and ingested bacteria in the other medium. No such observations have been made in spite of numerous attempts. It is difficult to be sure

that no bacteria are present in the amebae so that in this case the evidence is not conclusive. If tissue cells or cell fragments were being ingested in the tissue-bearing subtrate, they should be demonstrable; thus this negative finding is more conclusive.

A second possibility is that the presence of the tissue or bacterial cell provides a set of conditions conducive to propagation of *E. histolytica*. In such a situation, ingestion of these cells would not be necessary. Their presence in an otherwise nutritious substrate would be sufficient for the promotion of propagation of the amebae. The conditions would be physico-chemical in nature and would not necessarily depend upon the presence of a single chemical substance, but might depend on a series of substances arranged in a definite pattern. Such a pattern might be broken up by disruption of the tissue cells as in the experiments described above where such material was tried. Certain preliminary experiments indicate that disrupted bacterial cells also do not support propagation of *E. histolytica*[11].

Much more information is necessary before a complete description of the growth requirements of *E. histolytica* can be given. The critical problem now is to ascertain the true contribution of the bacterial cells on the one hand or of the tissue cells on the other. Of the two, it would appear that the easier one to investigate is the bacterial cell.

Conclusions

The above discussion is designed to present amebiasis as a diagnostic and research problem and to show the need for developing a better understanding of the disease. The development of better diagnostic tools is the critical need in the clinical field. A simple serological test would fill a great need, but this has had to await advances in the ability to culture the causative agent under the proper circumstances. This, in turn, has depended upon information that can only be derived from extensive and careful studies of *E. histolytica*. More definitive studies of *E. histolytica* will, in all probability, lead to a better understanding of the pathogenesis of the disease and may indicate means of improving treatment. It is not meant to imply that the situation that now exists, confusing as it seems, is hopeless without further possibility of advances. Much valuable information is available and useful and usable means of diagnosis and treatment are available. It has not been possible to review here all the contributions of numerous clinical and laboratory workers who have, despite difficulties and limitations, contributed greatly to the knowledge of amebiasis.

There are now available research tools which, it is hoped, will be useful in developing new diagnostic methods and means of treatment.

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HORMONE THERAPY IN RHEUMATIC DISEASES*

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The following comments summarize opinions presently held by the writer on aspects of therapy of rheumatic diseases by means of adrenal and pituitary hormones. In this review a variety of topics is covered and pertinent therapeutic experiments are cited. These studies were undertaken four years ago at a time when it appeared that neither cortisone nor the pituitary adrenocorticotropic hormone would prove useful in the usual sense as a therapeutic agent. Both of these hormones were thought to be dangerous, and a long-continued therapy based upon their administration seemed unlikely to prove practicable. As the work progressed however, it became apparent that this conviction would need to be altered. In order to maintain immediate benefits achieved by many patients, continued administration of one or the other appeared to be unavoidable. Passage of time showed that the human organism can usually tolerate long-continued administration of these agents. For many persons, such continued administration was a means of rehabilitation after months or years of invalidism. For some, long-continued administration appeared to be a life-saving procedure.

In the beginning of this work it was anticipated that physiological experiments might lead to discoveries of agents both useful and safe. In the end (if the present may be looked upon as at least a temporary "end") these hormones are of themselves decidedly accepted as therapeutic agents. Uncertainties concerning future consequences of long-term application remain, but these uncertainties have had to be endured and the work has had to be continued simply because of the press of circumstances. Long-term experimentation with human subjects has had to be pursued because no alternative course was possible and because an experimental animal is not available to provide a substitute for the human subject. Patients who were greatly improved by this therapy could not be abandoned, so to speak, in mid-air because of nameless fears. The alternative to continuing would be progression to hopeless invalidism for some persons and death for others. Regardless of what future developments may reveal in the way of advancing knowledge in this field, it is plain to see that hormones are in fact today widely established as therapeutic agents. Their use is an accepted procedure in medicine, not only for brief and heroic moments but also for long and patient administration.

Certain principles if kept in mind facilitate the use of these agents, and increase both the safety and effectiveness of their administration. It is with these principles that the present paper is most concerned.

Nature and Action of ACTH

Adrenocorticotropic hormone is a protein-like substance made up of amino-acids conjugated into relatively larger molecular aggregates. The molecular weight of this substance ranges between ten and twenty thousand. Conjugation of the smaller amino-acid molecules into larger protein-like molecules is achieved by union between carboxyl groups and amino groups with simultaneous elimination of a molecule of water. Hydrolysis of adrenocorticotropic hormone with the aid of pepsin and hydrochloric acid yields polypeptides first and ultimately a number of amino-acids. Some fractions of this hydrolysate have been shown to possess powerful adrenal cortical stimulat-

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ing properties; however, products of hydrolysis have not been made available for clinical use.

In the human organism, pituitary adrenocorticotropic hormone is produced as a result of metabolic activities of basophilic cells within the anterior lobe of the pituitary gland. Indeed, certain aspects of the action of adrenocorticotropic hormone can be observed in patients suffering with functioning tumors of the basophilic cells of the anterior pituitary, suggesting that adrenocorticotropic hormone is at work in that condition also.

Extraction has been made commercially practical because of the relative ease with which solution occurs in water and in physiologic saline solution. From aqueous solution, the potent material may subsequently be precipitated either by addition of organic solvents or by electrolysis. The desiccated powder derived from such extractions is stable and may be sterilized without a notable loss of potency by use of ultraviolet irradiation.

A complex mechanism regulates the production of adrenocorticotropic hormone. Excitor stimuli arising in the hypothalamic nuclei act as the immediate stimulus and the hypothalamic nuclei are in turn attuned to body needs through a mechanism which is brought into action by chemical agents circulating in the blood. Products of either cellular attrition or inflammation, as well as epinephrine act as stimulants of this mechanism. Also potent as a stimulant is a lowering of the level of circulating adrenal cortical steroids. A high level of adrenal steroids in the blood appears to depress this action. The homeostatic mechanism which results from these checks and balances is in many respects comparable to the equilibratory mechanism by which the body maintains a satisfactory level of insulin production and carbohydrate metabolism.

Detection of adrenocorticotropic hormone in the blood has not been achieved, possibly because this substance is immediately utilized and disposed of after its release from the anterior lobe of the pituitary gland. The only site of its action thus far detected is the secretory zone of the cortex of the adrenal gland where, following administration of adrenocorticotropic hormone, there occurs a prompt lowering of ascorbic acid and cholesterol content. A conversion to corticosterone and subsequently to cortisone in all likelihood accounts for the disappearance of cholesterol. Significance of the lessening levels of ascorbic acid is not understood though it is probable that this substance is also utilized in the chemical synthesis of steroid hormones. Shortly after adrenocorticotropic hormone is administered it is possible to demonstrate in laboratory animals increased levels of adrenal steroid hormones in blood withdrawn from the adrenal veins, another fact which strengthens evidence of a prompt and effective stimulating effect on the cortex of the adrenal gland.

Developments in the field of pharmaceutical research have resulted in notable improvements in quality of the adrenocorticotropic hormone now available for commercial distribution. Potency has been greatly augmented, and today glands yield larger numbers of hormone units than was the case earlier in this work. In addition, prolongation of action has been achieved through addition of gelatin which reduces the rate of absorption. Products now available are relatively free of allergens and no longer show contamination with pitressin. These constitute important improvements, for during the early months of these experiments, materials available commonly caused urticaria or other allergic manifestations and not infrequently caused abdominal griping reflecting the presence of pitressin. In all likelihood, some products presently available contain some intermedin; hence, tanning or pigmentation is not uncommon in patients who are undergoing long-continued treatment with adrenocorticotropic hormone.

Nature and Action of Adrenal Cortical Steroids

When blood is derived from the adrenal veins it can be shown that cortisone

and hydrocortisone are present. The latter substance is found to be present in considerably greater concentrations than is cortisone, whereas extraction of the glands yields a higher concentration of cortisone. These observations have been interpreted as indicating that the adrenal glands manufacture cortisone which is in turn converted into the reduced form, hydrocortisone. Presumably this reduction takes place immediately after release of cortisone and it is believed that hydrocortisone is the active agent at the ultimate tissue sites of action. Presumably also, hydrocortisone is the agent active in overcoming disease symptoms; hydrocortisone is the "physiologically active" hormone.

Certain chemical structural features of adrenal cortical steroids have been observed to be essential to the quality of anti-rheumatic action. The basic molecule is the cyclopentanophenanthrene ring. This ring must be provided with an oxygen atom at positions 3 and 11. A double bond must be present at position 4—5. A hydroxyl radical must be appended to carbon atom number 17 and to this same carbon atom must be attached a side chain having the composition $— C = O — CH_2OH$. Deletion from the molecule of these features results in marked reduction or complete loss of therapeutic effectiveness.

Cortisone and hydrocortisone are only slightly soluble in water. This solubility is so slight that preparation for intramuscular and intravenous use cannot be achieved by water solution. Preparations in the form of microsuspensions have been devised and are satisfactory for parenteral use.

Cortisone and hydrocortisone are resistant to destruction by digestive juices of the stomach and intestine, and hence are not altered chemically when taken by mouth. Passage through the liver is likewise accomplished without an alteration of the molecule; hence, oral administration is effective for both compounds.

The chemical fate of cortisone and of hydrocortisone remains unsolved. Following intravenous administration there occurs rapid disappearance from the blood, so that within one hour blood levels return to normal. Both enteral and parenteral administration result in an augmented excretion of 11 and 17 oxygenated steroid compounds in the urine, but the amounts excreted are relatively minute, far too small in fact to indicate that urinary excretion is the fate of these compounds. Following the administration of 100 milligrams of cortisone, for example, the daily excretion of ketosteroid compounds increases from the order of 100 or 200 gamma, up to 400 or 600 gamma, only a few tenths of one milligram. It appears therefore that some internal destruction must take place. However, the site of this destruction and the chemical pathways involved have not been determined.

Mode of Action of Adrenal Steroids in Rheumatic Disease

In regard to this important question, only some meager generalizations are justified at the present time. To some extent these compounds exert a general anti-inflammatory effect which extends beyond the circumscribed diseases which we are presently designating as rheumatic. For example, in thyroiditis, ulcerative colitis, tuberculosis, and in some instances of pneumonitis, distinct anti-inflammatory action can be detected. This action against inflammation does not, however, explain the manifold effects observed in rheumatic diseases.

Up to the present, a deficiency of adrenal cortical hormones has not been found in rheumatoid arthritis. Therefore it does not appear that this is a replacement therapy. There is in fact no sign pointing definitely to an endocrine dysfunction among these individuals. Only recently an unusual steroid compound, 17-hydroxypregnanolone, has been detected in the urine of patients with rheumatoid arthritis but the significance of this finding is not yet apparent and it cannot be assumed to prove the existence of an endocrine abnormality.

Treatment of rheumatoid arthritis with adrenal cortical hormones has been described as treatment by induced hyper-

cortisonism. However, notable relief of these diseases is commonly achieved without any semblance of hypercortisonism; hence, the designation hypercortisonism would appear to imply a phenomenon which is not requisite for the achievement of therapeutic benefits. By no means is it necessary to induce the picture of Cushing's syndrome; rounded facies, hirsutism, hypertension, altered carbohydrate metabolism, water retention, abnormal fat deposits, and so forth, in order to relieve symptoms of rheumatoid arthritis. On the contrary, these symptoms may be looked upon as evidence of faulty administration, or overadministration and every effort of the therapist should be aimed towards preventing these toxicities or side-effects.

Precise means for measuring ability of the organism to respond to various stresses are not available. However, reaction to administration of epinephrine does not differ in rheumatoid arthritis from non-arthritic individuals. Ability to withstand heat, cold, surgical procedures, anesthesias, and trauma is not notably altered in rheumatoid arthritis.

Hormone Therapy for Rheumatoid Arthritis

Hormone therapy for rheumatoid arthritis is not a matter of days or even weeks. On the contrary this therapy has generally extended itself over periods of months or even years and because this is the case, hormone therapy for rheumatoid arthritis should be looked upon as of considerable gravity, not to be undertaken lightly by either the physician or the patient. During the course of hormone treatment patients are exposed to complex physiologic changes and should have the benefit of meticulous observation by a physician to reduce risks and hazards. To avoid complications and toxicities it is necessary that the patient be examined at regular intervals. Blood pressures have been observed to undergo notable increases; therefore, blood pressure should be checked and rechecked. Edema has been observed to wax and wane during treatment and may be controlled by various diuretic agents. There is a hazard of inducing hyperglycemia or glycosuria in occasional instances, therefore there is need for frequent urinary testing. The rheumatoid arthritis has in some instances increased or decreased in severity during the course of treatment, therefore requiring alterations in intensity or amount of therapy. These are but a few of the problems which have been encountered and which require constant consideration and detailed supervision throughout the entire period of treatment.

The complexity of this undertaking is not beyond the skill of most physicians. Close cooperation between the patient and physician has been the prime essential to safety and success during this procedure.

Choice of a Hormone for a Given Patient

Cortisone has been the more frequently chosen compound for long-continued treatment of rheumatoid arthritis, reflecting a lower cost of cortisone and its effectiveness on oral administration. Potency of both cortisone and the adrenocorticotropic hormone has been constant and both are now being supplied in stable forms suitable for every-day use. Both cortisone and the adrenocorticotropic hormone have been equally effective from the standpoint of effecting improvement of rheumatoid arthritis. Both have been well tolerated by numerous patients during prolonged administration. Problems of side effects and toxicities have been of equal severity and have occurred with equal frequency during use of both hormones.

Employment of hydrocortisone for oral therapy of rheumatoid arthritis is effective and practical. Clinical testing of the past two years has indicated the effective dosage for hydrocortisone to be approximately two-thirds to three-fourths of the amount of cortisone required under the same circumstances. However, slight advantages accruing to the patient from the somewhat greater effectiveness of hydrocortisone are today approximately offset by the notably higher cost. Other possible advantages of hydrocortisone are

a somewhat lessened incidence of side-effects accompanying smaller doses, also, in some instances "smoother" quality of symptom control. Exact evaluation of these aspects of hydrocortisone must, however, await further clinical experimentation and testing.

Intravenous therapy of rheumatoid arthritis with adrenocorticotropic hormone is at present only of theoretic interest. Immediate control of symptoms has been readily achieved by this procedure; however, prolonged control requires repeated daily administration, manifestly impractical for intravenous therapy except during limited periods.

Prolonged intramuscular treatment with adrenocorticotropic hormone has generally required that the patient administer the injections to himself, or a family member may be instructed for this purpose. For patients with severely damaged joints of the hands, self-administration has been impossible because of difficulty in handling the syringe, and in such instances intramuscular therapy was impractical unless the patient had constant attendance. Where these problems posed no weighty objection however, prolonged treatment with adrenocorticotropic hormone resulted in an extremely satisfying grade of improvement for many patients.

Short courses of hormone therapy for rheumatoid arthritis have rarely produced anything but temporary improvement; hence, patients should not be led to believe that cures will result after brief treatment. These experiments indicated that, prior to embarking upon a long-continued treatment with cortisone or with adrenocorticotropic hormone, physician and patient should discuss this therapy in some deail. It is advisable that the patient, and perhaps the family also, be informed that short courses and insufficient dosage will result in failure, that coincident ailments are neither more nor less frequent among patients receiving this therapy than in the general population. Coronary occlusions, superventon of arterial hypertension, peptic ulcer, thrombophlebitis and various infectious ailments have all occurred with expected frequency among hormone-treated patients. Upper respiratory infections, influenzal infections, sinusitis, cystitis, and many other problems were encountered, but these ran their usual course, responded as expected to standard therapy, and posed no distinctive problems in our patients. These accidents are not therefore sufficient justification to abandon hormone treatment.

Relapses During Treatment

During a course of hormone therapy for rheumatoid arthritis, some patients experienced relapses. Generally, though not always, relapses have signified insufficient dosage and have been relieved promptly when dosage schedules were adjusted. In some instances relapses during therapy were intense, accompanied by fever, severe aggravation of arthritis, prostration, tachycardia, and vasomotor disturbances. These called for heroic measures. The patient so affected sometimes required intravenous fluids to relieve dehydration and immediate resumption of hormone treatment in higher doses.

Character of Improvement

In most instances the effective therapy has been followed by notable improvement. Articular pain lessened, muscular stiffness receded, effusions tended to absorb, flexion deformities resolved to the extent that these were due to muscular spasms. In addition, when fever has been present, this symptom diminished, adenopathy lessened, subcutaneous nodules regressed in size and became less tender. While these changes occurred patients noted improved appetite, greater sense of well being, and greater muscular strength. Examinations of the blood disclosed a variable effect on sedimentation rates, often a fall towards normal and not infrequently alteration of serum proteins in the form of decreased levels of serum globulin.

Exceptionally, perhaps in one or two per cent of patients, extraordinary resistance to hormone therapy was encountered and no significant relief of symp-

toms was induced by either hormone or by combinations of both. This unusual resistance has portended a fatal outcome in some instances.

Termination of Hormone Treatments

Administration of either cortisone or the adrenocorticotropic hormone for periods of several weeks to a month or more sometimes induced a state of great sensitivity to withdrawal. A too rapid reduction of dosage, or too sudden cessation of treatment in such patients sometimes provoked a syndrome characterized by weakness, poor appetite, violent aggravation of arthritis, fever, tachycardia, and profound vasomotor disturbances. This picture has been likened to the "crisis" of Addison's disease. This syndrome has persisted for weeks or until treatment has been resumed.

The most violent aspects of this distressing reaction have generally been avoided by a very gradual withdrawal of hormone; however, even a slow withdrawal has been followed by a notable aggravation of arthritis in some instances.

This withdrawal syndrome is but poorly understood. On theoretical grounds it may be suspected that inertia, or functional atrophy of either the pituitary or of the adrenal gland is responsible, however a proof of this type of functional insufficiency has not been possible up to this time. It is probable that in most instances compensatory mechanisms are available to cope with withdrawal, provided the organism is given sufficient time to bring this protective apparatus into play. It is also likely that the withdrawal period is a time of unusual danger for the organism. During this period the organism may not be able to respond promptly or efficiently either to infections or to stresses involved in surgical procedures, and may not be capable of holding the process of rheumatoid arthritis in check. Hence, abrupt withdrawal of cortisone has been reportedly followed by otherwise unexplainable post-operative deaths. (None occurred in our experience, however several have only recently been reported.) Autopsies have shown, in these instances, adrenal cortical atrophy and, in one instance, adrenal atrophy together with hemorrhages, the so-called Waterhouse-Friderichsen syndrome. All in all, a considerable harm may result from the uncontrolled conflagration which takes place within joints when rheumatoid arthritis is thus permitted to go "out of control."

Long-term treatment with cortisone has more frequently been responsible for withdrawal toxicities than has treatment with the adrenocorticotropic hormone. Presumably, prolonged adrenocorticotropic hormone treatment, by bringing about an increase of adrenal size may compensate for whatever pituitary atrophy or regression may result from prolonged adrenocorticotropic hormone administration. Nevertheless, severe and even violent outbursts of rheumatoid arthritis have followed sudden withdrawal of adrenocorticotropic hormone and it may be assumed that, in such instances, other stresses may likewise find the organism unprepared, and unable to marshal adequate powers of defense or resistance.

Duration of Improvement after Cessation of Therapy

A withdrawal of either cortisone or adrenocorticotropic hormone, whether slow or abrupt, has generally been followed by a return of symptoms and aggravation of the objective phenomena of rheumatoid arthritis. This is a fundamental principle of cortisone and adrenocorticotropic hormone therapy and exceptions to this principle are only rarely observed. Recurrence after withdrawal has not been related to sex, age, location of articular involvement, duration of the disease, or duration of treatment.

Deterioration following withdrawal of treatment has not always progressed to the exact pre-treatment level. Often, some of the progress which has resulted has been maintained for periods of many months. A notable gain in weight has often been maintained and improved function has persisted in joints. Return

of articular pain and stiffness, however, has generally been accompanied by profound feelings of disappointment sometimes bordering on depression following withdrawal. Such disappointment can be avoided only by planning that will permit continued treatment for as long as may be necessary.

Potentiation of Cortisone and ACTH

Recent medical literature reflects a continuing search for agents to potentiate the potency of these hormones. Thus far however, this search has been fruitless. A long list of steroid substances and various non-steroid hormones has been tested without success. Particularly noteworthy have been our trials of desoxycorticosterone, progesterone, testosterone, insulin, thyroid extract, adrenalin, para-aminobenzoic acid, ascorbic acid, and pregnenolone. Testing of these substances by various observers resulted in differences of opinion during early months of the work; however at present, all have been generally discarded as ineffectual.

Although chemical agents have not been found effective for the purpose of supplementing the action of cortisone and adrenocorticotropic hormone, physical therapy, dietary management, removal of infections, regulation of rest and activity, and administration of gold have been regularly employed for these patients. Orthopedic measures including manipulations, employment of casts, braces and supports, arthroplasties, arthrodeses, synovectomies, and tendon transplants are as important today as ever before for a successful management of patients with this disease. Hormone therapy has brought a great advance, relieved much pain and ill health, but has not by any means reduced the treatment of rheumatoid arthritis to a simple matter of giving pills or administering daily injections.

Hormone Therapy of Still's Disease

Still's disease is rarer than the adult form of rheumatoid arthritis; hence, cortisone and the adrenocorticotropic hormone have not been as well tested among children as among adults. During the past four years however, twenty children with Still's disease were observed under treatment with these hormones, a number which is possibly sufficient to allow some modest generalizations.

Our experiences indicated that dosage requirements of children with rheumatoid arthritis are varied, as is the case in adults. In fact, the only generalization which seems applicable at this time relative to dosage is that requirements of children are somewhat larger than those of adults in proportion to body weight. Beginning doses ranged between one and two milligrams of cortisone for each kilogram of body weight and children with Still's disease usually required one to two units of adrenocorticotropic hormone daily per kilogram of body weight for effective control. Subsequent to the initial period of several days, it was usually necessary to adjust the dosage of either hormone upward in some and downward in others, as in adults.

Among the children who made up this group, side-effects from use of either cortisone or the adrenocorticotropic hormone were not more intense than in adults. Most frequently observed were water retention, rounding of the face, and excessive appetite with undesirable and unusual increase of weight.

Most of the children increased both in height and body weight in a satisfactory manner during treatment. Some were observed passing through the period of pubescence without incident. Female children began menstruation in a normal manner and secondary sex characteristics made their appearance according to the expected schedule. Growth of hair on the head and elsewhere proceeded normally.

A variety of additional treatment measures were employed. Physical therapy, occupational therapy, dietary manipulations, gold, and a considerable variety of orthopedic measures were used in most of the cases. The formula for treatment was never a simple one. For each child the problem was complex, ever changing and requiring continuing alterations of details.

Hormone Therapy for Spondylitis

The effect of cortisone and of the adrenocorticotropic hormone on rheumatoid spondylitis was comparable in most respects to that observed in rheumatoid arthritis of peripheral joints. In some instances in which spondylitis was especially severe, deformity marked, and the patient's general health greatly impaired, remarkable transformations were witnessed. Some individuals showed weight gains of twenty to thirty kilograms. Several returned to busy and useful occupations after months or years of seemingly hopeless invalidism.

Mobility of the spine was improved in most of the "early" cases but, in those who showed extensive bony bridging or calcification of intervertebral ligaments, little improvement of function resulted.

For the spinal form of rheumatoid arthritis, physical therapy was also employed in every instance. Orthopedic appliances were used as needed, the diet was altered as seemed necessary to bring about increases or decreases in body weight, and in some instances administrations of compounds containing gold was carried on in connection with the hormone therapy. Infected foci were searched for and removed as necessary.

Comments on Psoriatic Arthritis

Results of psoriatic arthritis therapy by means of either cortisone or the adrenocorticotropic hormone were in most respects comparable to results observed in the classic and uncomplicated form of rheumatoid arthritis. A lessening of articular inflammation occurred almost without exception, and relapses followed withdrawal with about the same degree of regularity as in the peripheral form of the disease. Our earlier observations among the patients of this group suggested that the skin manifestations of psoriasis are resistant to these hormones; however, when treatment was continued for as long as two to three years, most of the patients showed notable improvement of the psoriasis. Use of local therapy in the form of crude coal tar and irradiation with ultraviolet light, also sun-bathing, was employed in connection with the hormones. To some extent, therefore, response of the psoriasis in this group of patients may have been unusually good because of this local as well as the systemic therapy.

Results of Treatment of Rheumatoid Arthritis

After giving even a single dose of either cortisone or adrenocorticotropic hormone, a considerable improvement generally ensued and this improvement was at times both subjective and objective. When treatment was continued, further changes ensued. The extent to which this healing process progressed was varied. In some instances, almost every vestige of the disease disappeared. In some instances of rather severe rheumatoid arthritis, the disease was so successfully reversed that no signs of the disease remained. On the other hand, some patients continued to display intense symptoms of inflammation in joints, effusions, local warmth, pain on motion, and severe tenderness in spite of persistent administration of either cortisone or adrenocorticotropic hormone, or both. It was frequently observed that maximal improvement was not achieved at once, and often not until treatment was continued for many months. Results at the end of the second or third year have often been far superior to those observed after only a month or two of treatment, and patients were often in a far better condition at the end of long treatment periods than after a few weeks or months of treatment. In some instances, the patient did not achieve maximal improvement until treatment had been administered for two to three years. This writer believes therefore that treatment should be continuous and should be maintained as long a time as possible.

Observations made in this group of patients suggest that it is unwise for the physician to commit himself to any rigid plan of dosage at this time. Strongly advocated plans may fail in many instances. Short-term high dosage, alternating periods of cortisone with adreno-

corticotropic hormone, initial large doses followed by reduction of dosage to a very small dose, "maintenance" doses, interrupted courses, and so forth; all of these may succeed in some but not in all patients. None has been established clearly as the perfect schedule. At present, this writer prefers to start treatment of adults with approximately 100 milligrams of either cortisone or hydrocortisone, or with approximately eighty units of adrenocorticotropic hormone. Thereafter the daily dosage is altered by the method of trial and error, constantly seeking the least amount which provides adequate control and shifting from one to the other of these hormones if relapses occur in spite of intensive treatment with full doses. In a few patients satisfactory control has not been achieved with either hormone when given alone, but was brought about by administering both in full doses for several months to several years.

Interrupted treatment schedules seemed particularly destructive for some patients, resulting in repeated and often violent relapses during periods without treatment. Rigid adherence to any dosage plan would appear undesirable at this time.

Contraindications to this therapy have been sought but up to the present, there appear to be but few absolute contraindications. Both very young and very old patients have tolerated these hormones surprisingly well. Arteriosclerosis did not usually cause any particular difficulty. Diabetes mellitus was not notably affected in some instances. Hypertension was often not at all aggravated in spite of long-continued treatment. Old tuberculous lesions were observed to remain dormant even after several years of treatment. Intercurrent infections and healing of operative wounds progressed without incident. This writer believes that more important than a list of contraindications is the matter of studious and meticulous attention to the particular problems of each individual. Results have been rewarding in proportion to the cooperativeness of the patient and to the care which he and his family were able to devote to the project.

Treatment of Rheumatic Fever

The worth of either cortisone or of adrenocorticotropic hormone in treatment of rheumatic fever cannot be assessed as yet because of the variable evolutionary pattern of this disease, the tendency for relapses to occur followed by irregular periods of quiescence, and also because cardiac lesions often progress insidiously without reference to acute episodes detected by clinicians. No experiments performed thus far can escape the implications of these characteristics of rheumatic fever, and judgments seemingly plausible at present may well prove erroneous when judgments can be based upon longer observation.

In our experiences with rheumatic fever, acute attacks were regularly responsive to this treatment. We have repeatedly observed that fever resistant to salicylates responded promptly. It has been suggested, in fact, that this observation may be used as a diagnostic sign, that fever which fails to respond is in all likelihood not attributable to uncomplicated rheumatic fever and may indicate the presence of subacute bacterial endocarditis.

Other symptoms including sweating, pallor, poor appetite, prostration, and anemia have tended to remit promptly. A gain in weight occurred regularly. Tachycardia and articular pain generally disappeared promptly, as well as rheumatic erythema. Prolonged P-R interval in electrocardiograms generally returned toward normal within hours or a few days.

Subcutaneous nodules of rheumatic fever were evanescent in some patients but persisted as long as three to four weeks in spite of treatment in a few cases.

Both cortisone and the adrenocorticotropic hormone worked effectively in rheumatic fever. Hence we have chosen either one or the other in order to broaden the base of these observations. Adrenocorticotropic hormone was chosen

for the start of treatment whenever there was reason to believe that immediate results were needed, when attacks were violent, when fever was high, when the joints were intensely painful, when cardiac involvement was prominent, and particularly when heart failure was marked and seemingly based on active rheumatic inflammation rather than on old valvular deformity.

The manner and time of withdrawal of hormone treatment of rheumatic fever is a matter of considerable importance. To prevent relapses it seemed advisable to continue treatment for at least two weeks after all signs of the active process subsided. Withdrawal was accomplished slowly and in a step-wise manner, lowering the dose daily by ten or twenty per cent and, at the same time, keeping a close watch on the patient for signs of reactivation of the disease.

Prophylactic therapy with either penicillin or sulfonamides was undertaken as soon as the attacks were controlled and hormone therapy withdrawn.

Hormone Therapy of Osteoarthritis

Relief of the pain and articular stiffness was at times temporarily complete following administration of either hormone to patients suffering with osteoarthritis. As the work progressed, however, it became more and more evident that long-continued treatment of osteoarthritis with these agents is not generally practical. Anatomical alterations of osteoarthritis were not improved in any manner by this treatment, and symptoms often returned while treatment was under way. The outstanding achievement in osteoarthritis appeared to be the occasional marked lessening of acute pain. Relief from pain was observed in patients with morbus coxae senilis, osteoarthritis of the knees and spine, and in some patients with severely painful Heberden's nodes. It appears to the writer, therefore, that hormone therapy for osteoarthritis is at present best employed as a temporary adjuvant to intensive rest and physical therapy. It seems extremely important however, for those interested in research to take careful note of this remarkable phenomenon, a relief of symptoms in osteoarthritis, because this observation suggests that our understanding of the basic nature of osteoarthritis may well await progress of our knowledge in this field.

Therapy of So-called "Minor" Forms of Rheumatic Disease

Periarthritis of the shoulder is a complex subject and cannot be covered in brief comment because of the widely variable clinical patterns encountered among its various stages. In general, patients suffering intense pain from the acute form often responded brilliantly and with great suddenness to these hormones. In most cases, however, the results were incomplete and although major symptoms subsided, a degree of pain and limited motion persisted for weeks or months and required both physical therapy and other orthodox treatment measures. Patients with more chronic types of periarthritis, especially those with so-called "frozen" shoulder, reacted in a much less impressive manner. Patients whose muscles atrophied and in whom osteoporosis was present generally had mediocre results.

Tests were carried out in Dupuytren's contracture, epicondylitis, intercostal neuralgia, deQuervain's disease, painful plantar spurs, painful osteoarthritis of the bunion joint, prepatellar bursitis, and painful ganglion of the wrist joint. Results in these conditions appeared erratic and unpredictable. Occasional patients described relief of subjective symptoms but for the most part results were not impressive.

Hormone Therapy of Gout

There were many opportunities in this work during the past four years to confirm the observation that acute attacks of gout may resolve promptly after administration of these hormones. The matter of a practical application of hormones to therapy of gout is, however, not at all clearly established, judging from these experiences. In most instances, episodes of gout subsided promptly with such well-known meas-

ures as colchicine, salicylates, and dietary restrictions; hence, employment of hormones must be assessed in relationship to this older, proven therapy. We have observed so-called "rebound" attacks despite gradual withdrawal of hormones and recurrences of acute articular episodes in patients who were receiving "maintenance" treatments with these hormones for gout. Drawbacks to this hormone therapy for gout appeared weighty and the advantages only questionable.

Periarteritis Nodosa

Our own experience has closely corresponded with that reported during recent years from elsewhere. Hormone therapy relieved systemic processes and in some instances improved local phenomena such as articular inflammation and painful nodules. However, relapses occurred promptly following withdrawal, and deaths were observed during treatment. Necropsies showed fatal cardiac and renal damage supporting the view that healing engendered at the sites of arterial inflammation sometimes resulted in complete closures of these vessels. Our experiences leave no doubt, however, that in the presence of this regularly fatal disease this therapy, although attended with notable risk, offers at least a ray of hope and should be employed if at all possible.

Comment on Lupus Erythematosus

Among our patients, therapy of acute lupus erythematosus generally achieved rapid lessening of symptoms if the disease was of "average" severity. However, an estimate of relative mortality rates in treated and untreated cases may not be conclusive until at least another decade has passed. Until then, physicians will be justified in choosing to employ these agents wherever possible, even though it is recognized that remissions achieved may prove to be only temporary. This disease if untreated threatens immediate fatality in at least half the cases, thus hardly permitting any other choice. Deaths were observed, even during treatment, from renal failure, general toxemia, widespread systemic tuberculosis, and cerebral edema.

Recently proposed variations of therapy, intravenous therapy with adrenocorticotropic hormone and high dosage cortisone therapy, need further study.

Conclusions

Clinical investigations with hormones for this widely differing group of diseases progressed rapidly during the past four years and present experience permits some cautious preliminary conclusions.

Prolonged hormone therapy for rheumatoid arthritis has achieved results which far surpassed those obtained using older and orthodox therapeutic programs. Usefulness for other rheumatic diseases is well established for some and uncertain for others.

Employment of these agents is an undertaking which requires more than usual care on the part of the patient as well as the physician. Toxicities and side-effects must be reckoned with and weighed in the balance against possibilities of crippling invalidism for some patients or almost certain death for others. The situation calls for a sober realization that cures are relatively uncommon with this therapy but that older treatments produced even less satisfactory gains in an overwhelming majority of the cases.

A DIAGNOSTIC APPROACH TO THE PATIENT WITH ABNORMAL BLEEDING

IRVING A. FRIEDMAN, M.D.*

The systematic search for the cause of abnormal bleeding revolves around the simple concept of blood clotting. The fundamental formula for this mechanism is:

1. Prothrombin —> Thrombin
2. Fibrinogen and Thrombin —> Fibrin
3. Fibrin and Cellular Elements —> Clot

In the first reaction certain activators and accelerators are necessary for the conversion of prothrombin to thrombin. These factors can be represented as follows:

(a) Calcium
(b) Thromboplastin
(c) Plasma and Serum Accelerators

Prothrombin is a glycoprotein formed by the liver which apparently contains all the necessary amino-acid building blocks to produce the enzyme thrombin. This conversion, without accelerators, would take many hours; but as thrombin is formed it brings about the formation of more thrombin by inducing lysis of platelets with subsequent liberation of thromboplastin precursors. In addition, thrombin helps convert plasma accelerator to the more potent serum accelerator, and completes the clotting reaction by aiding the conversion of fibrinogen to fibrin. Once fibrin is formed, the cellular elements are enmeshed in its network and the blood clot results.

Importance of the Accessory Factors

a. *Calcium*: Only minute amounts of calcium are needing for clotting. For practical purposes a deficiency of this chemical never requires consideration. Even in the most severe hypocalcemic states, disturbance of clotting does not occur. Calcium is added to *in vitro* clotting tests to replace the calcium removed by the anticoagulant.

b. *Thromboplastin* is probably the most important accelerator involved in thrombin formation. It is a macromolecular lipoprotein which is not normally present in a free state in plasma, but during clotting is formed or activated from certain precursors. The major precursor of thromboplastin is found in the plasma and has been called *plasma thromboplastin precursor, euglobulin, anti-hemophilic globulin, Cohn fraction* #1, and *plasma factor*. Even slight deficiency of this factor may produce remarkable prolongation of the clotting time.

A minor precursor of thromboplastin is found in platelets and is probably liberated when they disintegrate. The absence or deficiency of this factor due to a decrease in platelets will not prolong the *in vitro* clotting time.

c. *Plasma and Serum Accelerators*

1. Major serum accelerator globulin (Major AC), also called Factor VI of Owren, is formed from plasma AC globulin (Factor V) under the influence of thrombin. This accelerator substance is measured together with prothrombin activity in the one-stage prothrombin test. If the one-stage prothrombin time is normal it can be assumed that both the prothrombin and serum AC globulin are adequate. If there is prolongation of prothrombin time, either or both of these factors may be deficient.

Deficiency of AC globulin may be differentiated from deficiency of prothrombin by adding excess AC globulin in the two-stage prothrombin determination. Absence of the serum accelerator factor will not cause prolongation of the clot-

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ting time, since other factors will compensate for this deficiency.

2. Minor accelerator globulins (Minor AC) have been identified by indirect techniques. A deficiency of these substances may occasionally cause a bleeding diathesis. This deficiency may be considered only when all other factors have been found to be normal.

The next reaction of the clotting process may be represented by the following formula:

Fibrinogen —› fibrin (plus cellular elements —› Clot

Thrombin again acts as an enzyme and converts fibrinogen into fibrin. Fibrin, together with red cells, white cells, and platelets forms the actual clot. Normally the clot retracts completely in a period of several hours, and the rate and completeness of retraction will depend on the number and integrity of the platelets.

Effective Use of Laboratory Procedures

Clinical evaluation is the most useful procedure in the diagnosis of the patient with abnormal bleeding. It often gives clues which lead to the appropriate laboratory tests for the prompt identification of the cause.

A careful history and critical examination of the patient, especially concerning the nature, location, and duration of bleeding, the appearance and distribution of petechiae and ecchymoses, and associated physical findings often give essential information.

However, the clinical picture may not be sufficiently clear, so that the determination of the integrity of the elements necessary for hemostatic equilibrium may have to be performed. Serious errors may be made clinically, especially when the cause of bleeding seems obvious, as in the case of hemorrhoids, menorrhagia, and epistaxis. Here, local therapeutic measures are attempted and the more serious underlying thrombocytopenia or other clotting or vascular defect may be overlooked.

a. *The Platelets*

The presence or absence of platelets can be determined very satisfactorily by the examination of a well prepared blood film. This simple method is as reliable as most techniques for the enumeration of platelets, which are unfortunately subject to considerable errors. The knowledge that the platelets are grossly deficient in number usually precludes the necessity for any further investigation into the cause of bleeding, unless there is some evidence for multiple clotting deficiencies. Numerical adequacy of the platelets excludes thrombocytopenic purpura of any origin but the appearance of the platelets gives no information as to functional platelet integrity. This means that the platelets may *appear* normal, yet have a marked defect in function, such as occurs in thrombasthenia.

b. *Prothrombin*

The one-stage prothrombin test is performed by adding thromboplastin and calcium to the plasma and timing the clot formation. This test, if normal, will rule out both prothrombin and AC globulin deficiency as described above.

The most common cause of hypoprothrombinemia is therapy with dicumarol or related substances which probably interfere with prothrombin formation in the liver, which are somehow associated with the action of vitamin K. Salicylates in large doses may act similarly to dicumarol. Prothrombin deficiency may be due to a congenital defect; infants may have low prothrombin levels after birth, since their gastrointestinal tract is sterile and lacks the bacteria necessary for vitamin K synthesis. Sterilization of the bowel with antibiotics will also similarly reduce vitamin K production and lead to hypoprothrombinemia. Profound liver disease may cause inability to form prothrombin with resulting severe hypoprothrombinemia; and absence of bile from the gastrointestinal tract from whatever cause will interfere with vitamin K absorption.

AC globulin activity may be decreased in severe liver disease or may be congenitally deficient. Dicumarol and related drugs have only a slight temporary effect on accelerator globulin activity. The routine clotting time would be nor-

mal where there is a deficiency in either of these substances, unless very severe depletion is present.

Patients with debilitating diseases often have some decrease in prothrombin activity without bleeding. Only profound reduction will cause difficulty. Errors associated with the technique of prothrombin determination are, of course, to be avoided. A common cause of confusion exists when the prothrombin activity is evaluated in the presence of heparin therapy. Heparin acts as an anti-thrombin substance and therefore causes a prolongation of clotting. This anti-thrombin action may cause confusion in the interpretation of the prothrombin determination in patients receiving both dicumarol and heparin therapy at the same time. The presence of heparin would give false prolongation of the prothrombin determination by chemically disturbing thrombin formation. Therefore, when heparin is used along with dicumarol therapy, as is commonly done, (since forty-eight to seventy-two hours are necessary for dicumarol to become effective) prothrombin determinations are invalid.

c. *Clotting time*

The only reliable method of determining the clotting time is by the Lee-White technique, the end point being clot formation in three serology tubes, each containing 1 cubic centimeter of venous blood. In several hours retraction of the clot normally occurs if the platelets are adequate in number and functional integrity. The venous blood clotting time is usually normal despite rather low prothrombin activity since very little of this substance is needed for the total reaction to occur in the glass tube, where variation depends on the smoothness of the glass surface, tissue thromboplastin, and other environmental factors.

If the major plasma factor (precursor to thromboplastin) is deficient, as is believed to occur in hemopilia, a remarkable defect in clotting occurs. On the other hand, a platelet deficiency will not in itself cause prolongation of coagulation *in vitro*. This platelet deficiency may either be quantitative or qualitative. In thrombasthenia there are normal numbers of platelets but they are functionally defective. In this relation we can easily understand the difference in the clotting, bleeding, and clot retraction time in hemophilia and thrombocytopenia or thrombasthenia. In hemophilia the clotting time is prolonged but bleeding time and clot retraction are normal, since the platelets are adequate; the vascular integrity is normal. The severance of a small vessel seals normally (bleeding time) in the presence of platelets and tissue thromboplastin and does not require the presence of fibrin. In thrombocytopenia the severed small vessel seals slowly because of the absence of platelets as well as some vascular or humoral defect, so that bleeding time and clot retraction are delayed. In thrombasthenia the qualitatively defective platelets may not adequately seal the severed vessel, causing a prolonged bleeding time and possibly a prolongation of clot retraction. Therefore for practical purposes, the clotting time will only be prolonged in hemophilia, afibrinogenemia, or heparin therapy.

Occasionally too much significance is placed on a slightly prolonged clotting time of twenty to twenty-five minutes. We have found in normal patients, with careful technique including clean glass tubing and minimal agitation during the test, that the clotting time may be as high as twenty-five minutes. At this borderline value much care should be taken not to diagnose hemophilia or to consider this supposed prolongation of clotting as a cause of the bleeding diathesis without further study.

d. *Prothrombin Consumption Test*

Occasionally the clotting time may be normal in hemophilia in spite of a decreased or absent *plasma factor* and the diagnosis is therefore difficult. Quick devised an ingenious test in which the consumption of prothrombin with clotting is measured in the period of an hour. In this test serial prothrombin times are performed on the serum (left with the clot) with the addition of a source of fibrinogen. Normally almost all the prothrombin is consumed and the prothrombin time will increase as shown in the

illustrative chart. If the plasma factor is absent or markedly reduced the prothrombin time will remain about the same within the hour period.

Prothrombin time in seconds after clot (illustrative examples)

	15 Minutes	30 Minutes	1 Hour
Normal	11 sec.	21 sec.	40+ sec.
Hemophilia	11 sec.	12 sec.	12-13 sec.
Thrombocytopenia	11 sec.	16 sec.	19 sec.
Thrombasthenia	11 sec.	18 sec.	20-25 sec.

Some reduction in prothrombin consumption will also occur in thrombocytopenia (absence of platelet thromboplastin precursor) and thrombasthenia but of much less magnitude. It has been argued that deficiency of AC globulin will influence the test but we do not believe this will give the clear cut values of hemophilia. This test is only of practical value in the diagnosis and evaluation of therapy of hemophilia when the clotting time is normal.

e. *Vascular Fragility Tests*

The simplest vascular fragility test is that of Rumpel-Leede, in which a blood pressure cuff is inflated midway between systolic and diastolic pressure and maintained at this level for fifteen minutes. The number of petechiae are counted on the forearm below the antecubital space in an area of a two and one-half cm. circle. In a positive test more than ten petechiae are found in the circle.

If the bleeding time is prolonged and other tests are normal, we are narrowed down to either a qualitative platelet defect (thrombasthenia) which may have a negative Rumpel-Leede test for vascular fragility and impaired clot retraction, or the nonthrombocytopenic vascular purpuras and vitamin C deficiency states, where the vascular fragility test is usually positive. This is often more of a clinical differentiation, since the thrombasthenic group may have only periodic prolongation of the bleeding time, and the vascular purpuras including scurvy may occasionally have normal vascular fragility and/or bleeding time tests.

It is also important to realize that multiple deficiencies in clotting can occur, such as is commonly seen in cirrhosis and nutritional deficiency states. The clinical picture will often give the best clues to these multiple defects.

Illustrative Clinical Examples

Thrombocytopenia: A male patient comes under observation because of a five year history of easy bruising, excessive bleeding with the slightest laceration, and with an acute episode of severe epistaxis, hematuria, and the presence of petechiae and ecchymoses over the legs, arms, and chest. Physical examination reveals the petechiae and ecchymoses described in the history and no other significant findings.

Clinically this patient demonstrates multiple bleeding areas which would very likely be associated with thrombocytopenia.

His peripheral blood smear should readily reveal the diagnosis in that few or no platelets will be seen in the blood film. We can anticipate that the bleeding time will be prolonged and the Rumpel-Leede test will be positive because of the platelet deficiency plus a humoral effect which is present in patients with idiopathic thrombocytopenia. Also, we would expect some decrease in prothrombin consumption. However, this test would not be necessary to make the diagnosis. Further studies, especially marrow examination would rule out marrow replacing lesions causing the thrombocytopenia.

Hypoprothrombinemia: A fifty year old male patient with a long history of alcoholism and malnutrition is admitted because of profound bleeding from the gums and frequent epistaxes.

Physical examination reveals a poorly nourished, slightly jaundiced patient who is quite ill. There are spider nevi seen over his chest and several ecchymoses on the arms and thighs; there is a sparsity of axillary and pubic hair and the patient has a moderate hepatosplenomegaly and ascites.

In this patient we would probably think of several factors contributing to

his bleeding tendency. The history of inadequate vitamin C intake as well as a positive Rumpel-Leede test would substantiate the diagnosis of vascular bleeding due to ascorbic acid deficiency (Scurvy). The prothrombin determination should be done and if found low, would indicate either a hypoprothrombinemia or AC globulin deficiency. Unless there is congestive splenomegaly and secondary "hypersplenism" associated with this patient's obvious cirrhosis, the platelets should be adequate. The only other consideration would include prolongation of the clotting time due to hypofibrinogenemia, rarely occurring in very severe liver damage. However, it is easily seen that the most likely cause of bleeding tendency here is a combination of vascular deficiency (scurvy) and hypoprothrombinemia.

Hemophilia: A boy with a family history of bleeding in several male members of the family is admitted because of severe hemorrhage after a tooth extraction. He gives a past history of pain and swelling of several joints after injury.

Here the first determination to be done is the Lee-White clotting time which may be very markedly prolonged and which will correlate with a marked decrease in prothrombin consumption. If the clotting time is normal a prothrombin consumption will substantiate the diagnosis. Here the platelets will be adequate, prothrombin determination, bleeding time, and Rumpel-Leede test all will be normal.

Thrombasthenia: A young woman gives a history of frequent epistaxes, menorrhagia, and severe bleeding after a recent tonsillectomy. Several other members of her family, including females, have had similar bleeding tendency.

Physical examination reveals no remarkable findings. There are no petechiae or ecchymoses.

In this patient, all the procedures mentioned would be normal except for the bleeding time and clot retraction, thereby substantiating the diagnosis of thrombasthenia. If there were more ecchymoses and the Rumpel-Leede test were positive we would consider a vascular defect more likely as the cause of bleeding tendency.

Summary

1. A simplified concept of the clotting mechanism has been presented.

2. The clinical picture in the patient with bleeding together with a few simple tests can readily evaluate the cause of bleeding.

3. The platelet determination, which can be simply observed on the stained peripheral smear, will immediately evaluate thrombocytopenia.

4. The prothrombin determination, when normal, rules out both prothrombin and AC globulin deficiency.

5. The clotting time and prothrombin consumption tests are needed only for consideration of hemophilia and the former may be prolonged in heparin therapy and afibrinogenemia.

6. In the presence of platelet adequacy and prolonged bleeding time, the clot retraction and vascular fragility tests can sometimes help to differentiate between "platelet defect" (thrombasthenia) and the vascular purpuras.

7. Multiple defects can always exist, such as is commonly seen in liver disease and nutritional deficiency states.

8. In most instances, clinical acumen and one or two well chosen determinations will suffice for rapid diagnosis of the cause of bleeding.

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TREATMENT OF NEUROSYPHILIS — A Review

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The problem of venereal disease control during the past war and pronounced changes in its therapy suggested a need for re-evaluation of the problem of treatment in neurosyphilis.[1,2,3,4] In approach the treatment of neurosyphilis, the first task is that of ascertaining the activity of the infection within the central nervous system.

Diagnosis and Classification

It is to be remembered that the presence of a positive serology is not proof of a luetic process. Confirmatory clinical signs and a definite history should be sought. Technical errors and serologic false positive reactions may result in the reporting of a syphilitic infection when none is present. Malaria, smallpox vaccinations, vaccine therapies for immunizations, infectious mononucleosis, and any acute infectious condition might be associated with a positive serology.

The following guides for determination of activity should be considered:

1. Clinical Symptoms:
   a. Signs and symptoms may be residuals of past destruction in a process now inactive.
   b. Improvements with therapy may be of a transitory character.
   c. Activity may be rather marked and the disease asymptomatic.
2. Spinal Fluid Reactions:
   a. A positive Wassermann in itself is not proof of present activity.
   b. Cell count, total protein, and globulin are indicative of activity when increased.
   c. Reactions of the spinal fluid vacillate during the first five years of syphilitic infection.
   d. A completely negative spinal fluid does not always indicate inactivity.
   e. A positive spinal fluid with an increase in cells and protein five years after an initial infection is a danger signal.
   f. In treated patients, the Wassermann and colloidal gold reactions may remain positive after the process is successfully checked. The protein and cell findings will then indicate the presence or absence of activity.
   g. The clinical signs of infection may be inhibited but spinal fluid activity is not permanently checked.
3. Blood Serologic Reactions:
   a. A negative blood serologic reaction following therapy for non-central nervous system syphilis when reversed by a positive finding suggests possible central nervous system activity.
   b. Failure of serology to become negative after treatment is not infrequent even though activity in the central nervous system is absent.

Spinal fluid findings may be used as a basis for evaluating the degree of activity; describing fluids as mildly, moderately, or severely affected. The criteria for classification recommended by the Syphilis Study Section of the National Institute of Health are given in Table I.

The classification of neurosyphilis as tertiary syphilis, with the following diagnostic nomenclature being utilized to specify the type of neurosyphilis, is used with some degree of uniformity:[5]

1. Acute syphilitic meningitis
2. Diffuse meningovascular syphilis
3. Vascular syphilis
4. Gumma of the brain or spinal cord
5. Optic atrophy
6. Tabes Dorsalis
7. Taboparesis
8. Psychosis with syphilitic meningoencephalitis (paresis)
9. Psychosis with neurosyphilis, other than paresis

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Degree Of Activity	Group	Cell Count	Protein	Complement Fixation
Minimal	I	7 or More	5-50 MG.	Negative
Moderate	II	7-200 or More	40-100 MG. or More	Positive .5 to 1 cc
Maximal	III	7-200 or More	40-200 MG. or More	Positive .1 to .25 cc

Table I

10. Neurosyphilis with other manifestations—specified as
    a. Nerve Deafness
    b. Erb's Spinal Spastic Paralysis
    c. Amyotrophic Lateral Sclerosis forms, *etc.*

The desirability of a routine investigation of all syphilitic patients to be placed on therapy is self-evident. An adequate physical examination and the usual routine laboratory investigations should precede therapy.

Therapy

The following is a general outline of therapeutic procedures in neurosyphilis to be used as a guide to a more extensive discussion:

I. Chemotherapy
    a. Antibiotic therapy
    b. Heavy-metal therapy—Trivalent Arsenotherapy — intensive and extended courses of treatment, pentavalent arsenicals, bismuth, iodides
    c. Combined therapy

II. Fever Therapy
    a. Biological
        1. Malaria — tertian and quartan
        2. Typhoid vaccine—multiple dose method, intravenous drip method
    b. External Radiant Heat
        1. Cabinet therapy, air heated units
        2. Other forms are seldom used at present

III. Combination Fever and Chemotherapy
    a. Fever with Penicillin
    b. Fever with Penicillin, Arsenicals, and Bismuth
    c. Fever with Arsenicals and Bismuth

I. Chemotherapy

Antibiotic Therapy

The introduction of penicillin in the treatment of neurosyphilis has been associated with encouraging reports.[6] At first, the length of treatment seemed to be as important as the dose. Various schedules[7,8] were worked out involving the use of injections of 40,000 - 50,000 units of aqueous penicillin every three hours for twenty-two days (150 - 180 doses).[9] More recently, penicillin with slow-absorption properties (procaine penicillin, with or without aluminum monostearate) has been introduced. This type of penicillin is less painful to administer, produces fewer local reactions, and can be given in larger single doses. At present, 2,400,000 units of procaine penicillin given every third day for four doses (9,600,000 units) is considered adequate for the treatment of symptomatic or asymptomatic neurosyphilis. Penicillin in the form of buffered tablets is unsatisfactory in the treatment of neurosyphilis.

It also has been noted that adequate penicillin treatment given during pregnancy[10,11] is nearly one hundred per cent effective in the prevention of congenital syphilis,[12,13] or in curing an already infected fetus *in utero.*

Most recently, other antibiotics have been used in the treatment of syphilis.[14] Aureomycin, either oral or intravenous, has been found as effective as penicillin in the treatment of early syphilis[15] and neurosyphilis.[16] Chloromycetin[17,18] and Terramycin[19] have had similar results.

Heavy-metal Therapy and Combined Therapy

Arsenotherapy, bismuth, iodides, and mercury have been largely replaced by penicillin alone or in combination with fever therapy in all cases of central nervous system syphilis. However, there are investigators who have shown that penicillin plus arsenicals and bismuth have a synergistic or additive activity in the treatment of syphilis, both experimentally[20,21] and clinically.[22,23] Another investigator[24] states that combination therapy has the same results as penicillin alone, but that the relapse rate is

less. In the combined therapy, ten to twenty mapharsen injections and ten injections of bismuth plus 6,000,000 to 9,600,000 units of penicillin are given. Since penicillin therapy has not as yet received acceptance by many as being satisfactory as a complete course of treatment, follow-up therapy with arsenicals, bismuth, and the iodides can be continued conveniently for six months to one year.

Conflicting reports as to the efficiency of penicillin in neurosyphilis are being explained on the basis of variability in the antitreponemocidal activity of forms of penicillin other than penicillin-G, which is considered to be the most effective.

Intensive arsenical therapy has been practically discarded due to the severe reactions and the high incidence of deaths.

II. Fever Therapy

The recognition of the importance of fever as a therapeutic agent in syphilotherapy is generally accredited to Wagner Von Jauregg. After trials with various agents used to produce hyperpyrexia, he finally resorted to malarial inoculations.

Fever therapy is definitely indicated in paresis and taboparesis and is considered the treatment of choice for tabes by some.[25] Malaria or other forms of fever therapy have not as yet been accepted as the treatment of choice for the mesodermal forms of neurosyphilis, but trends prior to the introduction of penicillin pointed to a widening of the scope of fever therapy for all forms of syphilis. The following chronic diseases are generally considered contraindications to fever therapy: tuberculosis, nephritis, carcinoma, and cardiac decompensation. Excessive obesity and severe malnutrition should be corrected before undertaking fever therapy. Aortic regurgitation is not a contra-indication, but patients having compensated regurgitation of the aortic valve should be given careful supervision. Tertian malaria is the most commonly used form.

Maleria Fever Therapy

The course of malaria seen is not typical for mosquito infection and is frequently quotidian instead of tertian. Temperature is sustained for periods of from one to three hours and then a gradual fall to normal temperature occurs with associated diffuse diaphoresis and exhaustion. The duration of the entire reaction is about twelve to sixteen hours. From eight to twelve fever paroxysms have been advised as the desired number for adequate treatment. Fever below 103°F. is usually not considered as a satisfactory paroxysm.

The general management of the patient during malarial therapy is essentially the management of any patient having intermittent fever and chills. Spontaneous termination of malarial fever may occur after the desired number of paroxysms have been obtained or may occur prior to completion of a satisfactory course of therapy. By use of intravenous typhoid injections of fifteen to twenty-five million bacteria, the malarial paroxysms may be reactivated. When sufficient fever therapy has been given or untoward response makes termination of therapy desirable, the use of quinine, atabrine, and newer antimalarial drugs, as in acute malarial attacks, is advised. In some instances, it may be found advisable to modify the course of the treatment to avoid a severe debilitating reaction due to the fever.

It has been suggested that a second course of malaria be given in some instances. Reinoculation has usually been unsuccessful unless carried out within three months of the first inoculation or after five years have elapsed. This immunity to tertian malaria is not associated with immunity to other forms. Quartan malaria therefore may be used during refractory periods. Where the clinical condition of the patient requires that the malarial therapy be cut short, two to three days of quinine therapy or other antimalarial drugs may be given to stop the paroxysms. Reinoculation may be carried out two to six weeks later.

Typhoid Vaccine Fever Therapy

Past experience has shown that cabinets or other artificial pyrexia-producing devices are frequently unavailable,

or if available, are lacking trained personnel. Malaria strains are often difficult to obtain or the patient may be nonresponsive to malaria. Typhoid vaccine fever therapy is almost invariably discarded by a large number of physicians as of little value because of the absence of effective or prolonged fever when it is used. The desirability of using typhoid vaccine when other agents are not readily available is worthy of consideration and it has been reported as being a very effective means of obtaining results in neurosyphilis[26].

Typhoid vaccine has several advantages over malarial therapy which must be considered in advising fever therapy. Although Moore's opinion that malarial therapy is more effective than therapy with foreign protein is generally accepted, it has been the authors' experience that clinical results seem to justify the conclusion that hyperpyrexia with typhoid vaccine may be as effective as that with malaria. The following advantages for vaccine therapy might be considered:

1. Ready availability
2. Control over the time and the severity of fever reaction
3. Less morbidity and mortality — almost to the point of being a negligible factor
4. Absence of immunity factor as seen with malaria in the Negro
5. Diminished nursing care, expense, *etc.*

The material used in treatment is that supplied by commercial firms for typhoid-paratyphoid inoculations or that supplied by the various public health service units. Vaccine prepared by various public health organizations contains one thousand million bacteria per cc. For administration, dilutions are made to contain ten million to one hundred million organisms per cc. for use in the first treatments given. As the dosage is increased, the undiluted vaccine is used directly. The injections are given intravenously.

Several methods of administration of the vaccine have been described. The recently described method of Solomon and Somkin probably deserves more recognition than has been given to it in the literature. This method involves the continuous intravenous infusion of the vaccine suspended in saline. The rate of infusion is adjusted so that a chill occurs in the first thirty-five to forty-five minutes. From this point, the temperature may be sustained at the effective level of about 104°F. for as long as six to ten hours without further chills by adjusting the rate of flow of the infusion. The maximum temperature elevation usually occurs within one and one-half hours after the chill.

The definite possibility of control of temperature and maintenance of temperature elevations for several hours is a distinct advance in biological fever therapy. The therapeutic results following typhoid vaccine fever therapy have not been considered equal to those obtained by using malaria or artificial fever as the therapeutic agent. However, the therapeutic results obtained by the use of ten to fifteen hyperpyrexic reactions and daily administrations will probably parallel those of malarial therapy.

Other Fever Producing Methods

The use of electric currents[27] to produce heat may be divided into:

1. External radiant heat
   a. Electric blankets[28]
   b. Electric light cabinets
   c. Cabinets with units for heating air
2. Penetrating heat (high frequency currents)
   a. Diathermy
   b. Radiothermy
   c. Electromagnetic induction

The use of cabinet fever therapy, which has to a large extent replaced all other forms of mechanical fever, is justified only where trained medical and technical personnel are available. Air conditioned cabinets have an advantage over penetrating heat in that burns are less apt to occur and technique of administration is somewhat simpler.

III. Combination Penicillin and Fever Therapy

The use of penicillin with fever therapy[29] is recommended especially for patients with general paresis, optic atrophy, tabes dorsalis, syphilitic nerve deaf-

ness, syphilitic non-paretic epilepsy, and Erb's spastic spinal paralysis. Penicillin does not interfere with the fever produced by malaria[30] and is started with the first elevation of temperature and is continued for ten doses. The same general plan is followed for penicillin therapy in combination with any of the other methods of fever therapy[31].

Follow-up Care

It is desirable that prolonged, regular post-treatment observation be maintained. In all cases, a neuropsychiatric examination, a serologic test for syphilis, and an examination of the spinal fluid should be done every three months during the first year after treatment, every six months during the second year, and at yearly intervals thereafter, indefinitely.

It is difficult to establish definite criteria of failure of therapy in symptomatic neurosyphilis, since clinical response depends upon the type and severity of the involvement of the nervous system. Certain signs and symptoms are the result of irreparable damage to parenchymal tissue and treatment can be expected to influence them little, if at all. Ordinarily, the most satisfactory therapeutic response will be observed in cases which originally showed "activity" of the spinal fluid, *i.e.*, an elevated cell count and total protein.

The following should be considered evidences of failure and indications for retreatment:

1. Appearance of symptoms and/or neurologic or psychiatric signs indicating progress of the disease to a symptomatic phase.
2. Increased degree of abnormality of the spinal fluid, especially an increase of cells and protein, at any post-treatment examination.
3. Cells and protein in spinal fluid are definitely abnormal six months after treatment.

Management of Treatment Failures

The treatment schedule used should be, generally, the same as the one used in the initial therapy. Cases originally treated with penicillin alone should be treated, with few exceptions, with combined malaria and penicillin, if the physical condition of the patient justifies the risk.

Where combined malaria and penicillin was used in the original therapy, retreatment generally should be with penicillin alone. An occasional case may require repetition of the combined fever and penicillin course. The latter is especially true of cases in which the first course of fever was unsatisfactory or inadequate.

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Abnormal Bleeding —

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CLINICOPATHOLOGIC CONFERENCE

Presented at Mount Sinai Hospital, Chicago, Illinois

DR. L. EDIDIN, Chairman DR. I. DAVIDSOHN, Secretary

Abstracted by DR. I. KACIONIS

Clinical History

First Admission: This forty-three year old white female entered Mount Sinai Hospital for the first time on March 27, 1949, with a history of a painless swelling over the right side of her face. It did not cause any particular difficulty and there were no associated genito-urinary symptoms. Shortly after that, the patient started to gain weight and her family doctor placed her on a reduction diet and thyroid medication. About one and one-half months prior to hospital admission the patient developed a pressure feeling in the lower part of her chest upon lying down. At the same time, her breathing became heavier on walking and on other exertion. There was never any history of hypertension, palpitations, or precordial pain. An electrocardiogram taken at that time was normal and x-rays showed the presence of fluid in both chest cavities. Her past history revealed the patient to have had a cough with some expectoration of phlegm for many years. Ten years previously she had a dermatitis which persisted for three years and finally remitted under various kinds of treatment. In addition, the patient had had "nasal trouble" with frequent episodes of epistaxis for many years.

Second Admission: The patient was readmitted to Mount Sinai Hospital on May 20, 1949. During the eight weeks between her first and second admissions the patient underwent five thoracenteses. Streptomycin was received daily in the last two weeks of this period. However, dyspnea and a choking sensation persisted.

Physical examination revealed the patient to be in no acute distress, but she was slightly dyspneic when lying down. Examination of the chest revealed the left breast to be larger and firmer than the right, but non-tender. Percussion and auscultation of the lungs revealed flatness and decreased breath sounds in the left and right bases posteriorly and anteriorly. No rales were heard. The heart was within normal limits. The pulse rate was eighty beats per minute and occasional extrasystoles were noted. The blood pressure was 130/70. The abdomen and extremities did not show any abnormalties. On June 6, 1949, bronchoscopy and bronchial biopsy were performed. The pathological report was negative. On June 21, 1949, a biopsy of the left breast was performed with removal of a deep wedge of breast tissue from the "six-o'clock" region. The pathological diagnosis was: Fibrocystic disease. The patient's chest was aspirated a number of times and 1,000 to 1,100 cc. of straw-colored fluid were obtained on each occasion. The patient was discharged on June 23, 1949, with the suggestion of readmission for an exploratory thoracotomy if it should become necessary.

Third Admission: The patient was readmitted to Mount Sinai Hospital on April 1, 1950, after she had spent several months at Michael Reese Hospital in Chicago, Winfield Hospital, and the Mayo Clinic, where all diagnostic tests available were done to determine the cause of her bilateral pleural effusion. She came to Mount Sinai Hospital at this time for establishment of permanent drainage of the pleural cavities. The surgeons were of the opinion that there was no indication for exploratory thoracotomy, in view of the symmetrical distribution and the absence of visible lesions radiographically.

Physical examination revealed a forty-four year old white female who was not in acute distress. Examination of the head and neck was essentially negative. Examination of the lungs revealed dullness to percussion at the right and left lung bases, more pronounced on the left side. The breath sounds were suppressed at both bases and a few rales were heard above the fluid levels. The

LABORATORY DATA

Blood counts:	RBC (mill.)	Hb. (Gm.)	C.I.	WBC	Differential Count (in %) Stabs	Segs	Eos	Bas	Lymphs	Monos	Direct Eosinophil count
3/27/49	5.34	14.4	0.87	6600		73	1	1	24	1	
6/1/49	4.8	14.4	0.96	5100		78	1		20	1	
4/1/50	4.67	13.0	0.89	5900		72	3	2	19	4	
7/1/50	3.99	11.9	0.96	6400		80	5		11	1	
1/11/51	4.50	13.0	0.91	8300		88			6	6	78/cu. mm.
1/7/53	4.50	11.8	0.84	10000	1	90	2		6	1	

Blood chem:	T.P. (Gm)	Alb. (Gm)	Glob. (Gm)	Ceph. Floc.	Sugar (mg/100 cc.)	BUN	Chol.	Chol. Est.	Alk. Phos.	Ca. (mg/100cc.)	P.	Thymol Turb.
3/29/49	6.4	4.7	1.7	Neg.	76	14.5						
5/21/49	5.7	4.3	1.4	Neg.	83	15.1	276	80%	58.9			
6/1/49									61.6	9.0	3.6	0
4/11/50	5.1			2+	83	12.3	269	58%	37.8	10.1		0
7/1/50	5.4	3.7	1.0	Neg.	89	15.1	304	69%				
1/12/51	6.3	4.4	1.9		108	12.3						
1/31/51					120							
1/8/53					75	15.1						

Urinalyses: Were completely negative on all admissions.

Miscellaneous tests:

4/24/49 Typhoid "H" & "O", Para A & B: Negative.
4/11/50 Bence-Jones Protein: Negative.
1/8/51 ESR (uncorrected) 24; Hematocrit 44.
Serologic tests for syphilis were negative on all admissions.

Bacteriologic examination:

Smear, culture, and guinea pig inoculations were done with sputum, bronchial smears, thoracentesis fluid, and gastric fluid on numerous occasions throughout the patient's illness and hospital course. No acid fast bacilli or fungi were ever seen and all guinea pig inoculations were negative for tbc.

Pathologic Reports:

6/6/49 Bronchus biopsy: No cancer cells seen.
6/21/49 Breast biopsy: Fibrosis, lobular hyperplasia.
Repeated examinations of gastric fluid, thoracentesis fluid, and sputum for cancer cells were negative on all hospital admissions.

X-rays:

3/28/49 Chest: Bilateral pleural effusion, more extensive on the left side.
4/5/49 Stomach: Stomach displaced to the left, probably by the liver. No intrinsic pathology of the stomach, esophagus, or duodenum. Enlarged right kidney.
5/21/49 Chest: Bilateral pleural effusion, more marked on the left side.
4/28/49 Colon: Colon normal. Spleen, liver and right kidney appear enlarged.
5/31/46 Laminogram: (1) A mass displaces the trachea to the right and causes narrowing of the left main bronchus; this is compatible with an intrapulmonary mass, but whether the mass is a primary or secondary neoplasm cannot be determined. (2) Bilateral pleural effusion.
6/2/49 Skull: Coarsened appearance resembles that seen in hyperparathyroidism. No metastatic lesions evident.
4/3/50 Chest: Bilateral pleural effusion, more prominent on the left. Associated pneumonic infiltration may be present on the right.
1/8/51 Chest: Bilateral pleural effusion and pulmonic infiltration above the effusion.

blood pressure was 100/70, the pulse was regular at a rate of eighty-eight beats per minute. The second aortic sound was greater than the second pulmonic. On April 9, 1950, a closed drainage of the left pleural cavity was established by insertion of a permanent catheter. For several days postoperatively the patient experienced relief of her dyspnea. However, she subsequently complained again of dyspnea, chest pains, and inability to sleep. Since the catheter provided no relief, it was removed after two weeks and frequent chest aspirations were made. On April 28, 1950, she was discharged as improved.

Fourth Admission: The patient was readmitted to Mount Sinai Hospital on June 30, 1950, with complaints of very severe dyspnea of four days' duration. Since the last hospital discharge she had had thoracenteses every week.

Physical examination revealed her to be in no acute distress. The blood pressure was 124/82, pulse was regular at a rate of eighty beats per minute. Both breasts were markedly enlarged and firm in all quadrants. The lungs manifested dullness in both bases with decreased breath sounds. No rales were audible. The heart and abdomen did not reveal any pathological changes. Examination of the extremities showed slight pressure edema. There was also a pitting sacral edema. On July 3, 1950, consultation with an allergist was requested. He had the impression that this was an allergic picture with angioedema of the face, breasts, and serous membranes. The possibility of hypothyroidism or early polyserositis was also considered. Basal metabolism studies done on July 7, 1950, revealed a rate of plus six. The patient was discharged on July 13, 1950, with advice to return to the allergy out-patient clinic for a future work-up.

Fifth Admission: The patient was readmitted to Mount Sinai Hospital on January 6, 1951, for the purpose of receiving ACTH therapy. Since her last admission eight months ago she had continued to require thoracentesis for the temporary relief of her dyspnea.

Physical examination revealed a well-developed, well-nourished forty-four year old female who appeared to be in no acute distress. The breasts were enlarged and quite hard, with a three plus pitting edema but no inflammatory reaction. Examination of the lungs revealed dullness on percussion, absence of breath sounds, and a few fine rales over the lung bases posteriorly. The heart sounds were of good quality and no murmurs were audible. The pulse was regular at a rate of seventy beats per minute. The blood pressure was not taken on admission. On January 11, 1951, the blood pressure was 114/84. The abdomen was obese but otherwise did not show any abnormal changes. Examination of the extremities revealed one to two plus pretibial pitting edema. On January 1, 1951, aspiration of both pleural cavities was done and one day later ACTH therapy was started (15 mgm. every six hours). Several days later, after treatment was begun, the patient appeared subjectively improved. She was breathing quite easily; whereas before she usually had been dyspneic four days after thoracentesis. The edema of the breasts diminished slightly. Examination of the chest revealed the presence of effusion bilaterally at approximately the same level as that following thoracentesis. On January 19, 1951, the fluid level rose again and remained at this higher level. Pathological examination of the pleural fluid revealed it to be negative for neoplastic cells. On Feb. 9, 1951, ACTH therapy was stopped because it had resulted in no improvement of the patient's condition. She was discharged from the hospital on February 11, 1951, with the recommendation of continued follow-up in the out-patient clinic.

Sixth (final) Admission: The patient was readmitted to Mount Sinai Hospital on January 7, 1953, because of extremely severe dyspnea and orthopnea.

Physical examination revealed her to be very dyspneic, but not cyanotic. Examination of the eyes, ears, nose, and throat was negative. Examination of the neck revealed a scar on the right side. The lymph nodes were not palpable. Both breasts were enlarged, the

right breast being hard and stiff. Percussion and auscultation of the lungs revealed dullness and absent breath sounds over both posterior lobes up to the scapular angles, above which there were some crepitant rales. Examination of the abdomen showed no abnormal findings except for a surgical scar in the right inguinal region. The patient had been operated upon for an inguinal hernia two weeks before at the Michael Reese Hospital. Examination of the heart was negative. The blood pressure was 110/80, pulse was regular at a rate of eighty-two beats per minute. The extremities were normal. No edema was noted. Treatment consisted of a number of varidase injections into the pleural cavity. Thoracentesis was done twice but no fluid was obtained on either occasion. On January 14, 1953, the patient was placed into an oxygen tent because of extreme dsypnea. On January 15, 1953, a chest aspiration was again done and this time 700 cc. of clear straw-colored fluid with some blood clots were removed from the right pleural cavity. Following this procedure the patient's condition improved markedly and she refused to take oxygen. Since the time of her admission she had been very apprehensive because of her dyspnea. Her doctor's opinion was that there was also a psychogenic factor involved which added to the severity of the dyspnea. A psychiatric consultation was therefore suggested. On January 23, 1953, the patient was extremely tense and anxious. She was afraid to go to sleep for fear that her lungs "would not work." On January 24, 1953, she was out of bed, sitting in a chair, when her respirations suddenly ceased. Blood pressure and pulse were unobtainable. She was pronounced dead at 7:30 A.M. on January 24, 1953.

Clinical Discussion

Dr. J. Freilich: First, a word about the inguinal herniorrhaphy. It sounds very bad after all the complaints she had, and after all the procedures she had done, to do inguinal repair, but the story was not quite as bad as all that. She had a mass in the right groin that had been noted for three to four months prior to her last admission and the diagnosis had not been accurately established as to whether the mass was a hernia, fat tissue, or lymphadenopathy. The diagnosis of hernia was made at surgery and I suppose it was repaired at that time.

This patient had a four year history of illness during which time the patient was completely symptom-free with the exception of her respiratory system difficulty, which was directly related to the amount of fluid she had in her pleural cavities. She had become dyspneic when both pleural cavities were filled with fluid. After they had been aspirated, she was quite comfortable. She had no complaints at all relative to any other system during this entire period. She was a rather good looking woman and for the entire period she looked well. There were no progressive changes during this four year period. The only specific complaint was that of dyspnea due to bilateral pleural effusion. So we are faced here with the problem of this woman being well except for one complaint, who over a period of four years had pleural cavities that were continually pouring out fluid on both sides and in quite marked quantities. The thoracenteses had to be done with increasing frequency and for the last several years she required a thoracentesis at least every two weeks, and sometimes every ten days. There was never any indication of inflammation of other serous membranes. She never had any pericarditis that we could find, and there was never any enlargement of the heart shadow or enlargement of the heart on physical examination. She never had signs of ascites. Occasionally she had slight edema of the lower extremities which we always felt was related to her low albumin. She received plasma on several occasions, with complete relief of the ankle edema.

Her course started here in 1949. She went from here, where no diagnosis was established, to the Mayo Clinic. There she was completely worked up, including thoracoscopy and a biopsy of her pleural membrane. The report came back as chronic inflammatory tissue and

no diagnosis was established. They had no opinion to offer at the time except the statement that in their experience unknown pleural effusion of this type was almost always of tuberculous etiology. It was suggested that she be sent to a tuberculosis sanitarium for a period of six months at bed rest with antimicrobial therapy in an attempt to find out if the effusion would disappear. They also made the statement, which we of course know, that bilateral pleural effusions in tuberculosis are rare as they are in almost any other disease that will be discussed.

The patient then went to Winfield Sanitarium for a six-month period of bed rest where I believe she was started on streptomycin and PAS therapy. At the end of that time the situation was unchanged, and it remained so for the next four years. She was then sent to Michael Reese Hospital for further work-up and examination. These tests were again all completely negative and no diagnosis was established. She was then in and out of this hospital and Michael Reese Hospital. There was no marked change in her course during any one of these hospital admissions and she was always readmitted because of an idea of making some diagnostic or therapeutic attempt. She died without a diagnosis being established.

One of the first diseases considered was heart disease, because that is one of the few causes of bilateral pleural effusion. She was investigated with the idea of diagnosis of heart disease but there was never any evidence of increased venous pressure or increased circulation time. Examination of the heart was always negative and there was never indication of congestive failure. Rheumatic heart disease with rheumatic pneumonitis and pleuritis was considered. Again there was no evidence for this. There were never any rheumatic manifestations, arthralgic episodes, enlargements, swelling, or redness of the joints, fever, increased sedimentation rates, etc. We never felt that there was a cardiac basis to account for the pleural effusion.

A variety of types of carcinomas were considered, but the length of the course with a lack of metastatic disease and the absence of neoplastic cells in the pleural fluid, plus the fact that there was no downward course for this period of time, allowed no one to entertain a diagnosis of carcinoma for any length of time.

Tuberculosis, of course, was considered from the start. However, bilateral effusions are rare. Acid-fast organisms were never found in the pleural fluid, and the course was not typical of tuberculous effusion. It should have cleared up on rest and antimicrobial therapy. The diagnosis of tuberculosis was not long entertained.

Meig's syndrome with pleural effusion was considered also. She had gynecological examinations by at least half a dozen competent gynecologists. Fibroma of the ovary or enlargement of the ovary could never be determined. At Michael Reese Hospital she had a pneumo-peritoneum with excellent visualization of pelvic organs and both ovaries; everything appearing normal. An exploratory laparotomy was considered at one time in order to investigate the ovaries, since we could not be certain that a small fibroma was not present, but the idea was discarded.

Then, of course, the collagen diseases were considered. Diagnoses of lupus erythematosus, periarteritis nodosa, and dermatomyositis were entertained since her first hospital admission here. She had biopsies of her skin, the pleurae, muscles, breast, and bones, none of which were diagnostic. The bone biopsy was done at Michael Reese Hospital from a fairly extensive lesion of the tibia. The conclusion was that there was nothing diagnostic in the bone and bone marrow that they had obtained. The diagnosis of collagen disease was hard to entertain in the absence of other suggestive findings. She had none of the chemical changes in the blood which we expect to see. Leukopenia, arthralgias, and manifestations in other systems never appeared. Her treatment with ACTH later,

was actually a therapeutic test.

Obstructive phenomena were considered since her first admission. No one would give any estimation of the location of an obstruction, but an obstruction of the venous system was considered. Azygous vein obstruction, superior vena cava syndrome, or a modification thereof, was thought of. Lymphatic obstruction was ruled out because she never had chylous fluid in the pleural effusion. Exploratory thoracotomy was considered at one time, but the idea was discarded.

An allergic disease was one of the possibilities. Allergic pleural effusions have been reported, as well as allergic pericardial effusions. Of course, the history is not similar to this case. They are usually secondary to respiratory infections and we never found any other allergic manifestations. There was no history of hay fever, asthma, hives, or other allergic diseases.

On her final admission to Michael Reese Hospital, granuloma of unknown etiology, multiple myeloma, and sarcoidosis were considered. Some lipoid metabolic disturbance was considered but no one cared to put a name on it and it was just thrown out as a last straw.

Diseases of endocrine organs were then considered. Thyroid and parathyroid disease were investigated fairly adequately. Myxedema with ascites as the only manifestation was considered at one time. If it was myxedema, it must have been a localized myxedema, since it certainly was not generalized. Her appearance was not that of a myxedematous person. She never had anemia, her basal was not low, her cholesterol was not high, and we could not find any other evidence at any time of hypothyroidism. She did have bone lesions consisting of defects in her skull and some of the long bones. I do not know which ones they were, although there must have been one of the tibia, because that was where the biopsy was taken. She never had laboratory evidence of parathyroid disease. I know she had calcium determinations of the urine, and calcium, phosphorus, and alkaline phosphatase studies of her blood, but I do not think that anyone at any time seriously entertained the idea that we were dealing with a hyperparathyroidism.

No definite diagnosis was established at the time of her death, but the patient represented a problem of treatment. Here was a woman who was entirely well, felt well, was mentally well, was able to take care of her home, etc., except that every ten days or two weeks she would become short of breath and would require thoracentesis. At first it was predominantly on the left side, then it became severe on the right side. From the very start however, there was always a bilateral effusion. No diagnosis was made, but an attempt was made to abolish the effusion, in some manner or another. It was hoped that fibrotic union would occur between visceral and parietal pleura, thereby obliterating the space and preventing the effusion. Dr. Mackler put a catheter in her left chest several years after this had gone on and drainage was established. Then it stopped draining, the catheter pocketed itself off and the effusion proceeded as before.

ACTH was used as a therapeutic test on the basis that this might represent one of the collagen diseases of undetermined etiology. This was tried in 1951, shortly after the introduction of ACTH, but I do not know if we can say that the dosage was adequate or the length of time was sufficient as far as her treatment was concerned. She received it only for a three week period and there was no effect on the course of her disease. It says in the clinical abstract that she was subjectively improved and I think that was probably the nonspecific action of the steroid. There was no effect on the quantity of the effusion. That was the only thing we were concerned with. She felt well enough without the ACTH. The subjective improvement was not anything that we had to have. We did had to have something that would stop the effusion.

For six months prior to her last admission, increasing difficulty was experienced in removing the fluid, and blood was obtained on several occasions. These were considered to be traumatic experiences. Because of the fact that the effusion was becoming loculated and was pre-

venting adequate drainage of the chest, we felt that proteolytic enzymes might be of value. We assumed that there were fibrinous deposits in the pleural cavity that were causing pocketing of the pleural fluid and we thought of using varidase, with the idea of lysing the fibrinous deposits to allow easier aspiration of the effusion. She received the proteolytic enzyme during her last admission, but the effects were nil. No liquefaction was noticeable and there was no evidence that the enzymes helped to alleviate her distress. That is the situation as far as diagnostic and therapeutic efforts are concerned.

Dr. Ellis B. Freilich: This case is certainly a challenge as to what the etiology might be. Dr. Joseph Freilich has given you a comprehensive discussion of the differential diagnosis. There are certain things that stand out to me; first is the fact that this woman maintained a good nutritional appearance during the course of her disease, which perhaps speaks against a systemic disease. Secondly, the findings at various hospitals were essentially negative. There were no positive findings to corroborate any of the entities that were discussed. Thirdly, here is a patient who maintains her nutrition, looks well, and has recurrent hydrothorax. There is the possibility that an obstructive phenomenon could be the cause of this condition. What obstruction? What could possibly cause this constant recurrence of bilateral pleural effusion. There is the possibility of interference with circulation. What could that be? There is one thing Dr. Joseph Freilich did not mention among his tentative diagnoses. I am thinking of a constrictive pericarditis. The reason I mention this is that there is an entity designated as Pick's disease, which consists of pericarditis, pericardial effusion, pleural effusion, and an enlarged liver. Although there is no pathognomonic sign indicative of constrictive pericarditis, this patient manifested obstructive phenomena without hepatomegaly or ascites. Such an obstruction may interfere with circulation in such a way that bilateral hydrothorax can occur. If you have a constrictive pericarditis, due either to rheumatic fever or an old tuberculous pericarditis, you have permanent interference with the circulation. In other words, neither rest nor drugs will help that particular situation. It is a mechanical situation and for that reason you can have constant refilling of the pleural cavity. Because of the fact that there was a permanency in this case, in a woman who had no change as far as her appearance or general condition are concerned, I venture the possibility of a constrictive pericarditis.

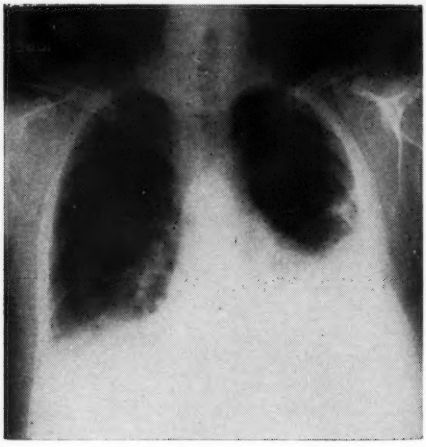
Dr. Harry F. Weisberg: The elevated cholesterol esters leads one to suspect some liver damage. The first report revealed a cholesterol level of 276 mg. per cent, with eighty per cent esters, and then there was a drop to fifty-eight percent esters during the third admission, at which time there was also a two plus cephalin flocculation. There may have been the possibility of some liver damage because later the cholesterol esters rose to sixty-nine per cent, which is within the normal range. It may have been a transitory hepatitis or some infectious process in the liver. I do not know if the enlarged liver on the X-ray coincides with that same date. The other thing I would like to mention is the point that Dr. Joseph Freilich made concerning the ACTH therapy. On January 1, 1951, ACTH was started. Five days later the blood sugar had increased to 108 and 120 mg. per cent on two succeeding occasions during the therapy. Prior to ACTH therapy, her blood sugar had been about eighty mg. per cent, and after the ACTH was stopped it had fallen to 75 per cent again. Thus we see the effect of ACTH on carbohydrate metabolism.

Dr. H. Kamin: An electrocardiogram done during 1950 revealed low voltage in leads I, II, and III, a nice S wave in lead I, and no S wave in leads III or AVL. Such findings are nonspecific and are compatible with bilateral pleural effusion.

X-ray Findings

Dr. J. Arendt: The chest films taken in 1949 show various stages of fluid accumulation in the pleural cavity on both sides. At times the pleurisy extends along the mediastinum and reaches the inter-

lobar fissure and forms an apical cap. When fluid is withdrawn the diaphragm appears particularly flat and flabby. We do not see evidence of malignancy or tuberculosis on either our films or those of the Mayo Clinic, which we had for comparison. A negative X-ray film, however, as is common knowledge, never rules out the presence of these processes in their microscopic or lymphangitic variations. The sputum was at all times negative, bronchography was negative,



Bilateral pleural effusion, more marked on the left.

and various examinations including X-ray studies at the Michael Reese Hospital, Winfield Sanitarium, and the Mayo Clinic were equally unsuccessful in demonstrating pathology underlying the recurrent pleural effusion. (See x-ray photo above.)

As to the other organs; the stomach was normal; the colon had a normal appearance; and the right kidney was large and showed the presence of a double ureter. The liver appeared to us to be slightly larger than normal. Its edge reached far down beneath the rib arch on the film taken in the recumbent position.

The bones, particularly the skull, showed marked decalcification or osteoporosis. The trabeculation was coarse and the bones had a groundless appearance, not expected in a patient of this age who was in a generally good nutritional state. These were not metastases, nor were they foci of myeloma, but a degree of osteoporosis as is seen in various conditions such as osteodystrophies of various types, hyperthyroidism, and Cushing's syndrome. All these conditions and many more may give osteoporosis of the skull.

As we followed the case at various stages, we found occasional bronchopneumonic foci which appeared and disappeared, recurrent pleural effusions, a small heart, and at times some pleuropericardial effusion. We found no definite evidence of malignancy and constantly gained the impression of a generalized systemic disease not accessible to radiological detection and diagnosis.

Autopsy Findings

Dr. I. Davidsohn: The pleural cavities contained 100 cc. of yellow turbid fluid on the right and 300 cc. on the left. Adhesions partly loculated the accumulations. The pleura, parietal as well as visceral, was greatly thickened. There was a slight excess of fluid in the pericardial sac, but none in the peritoneal cavity. Considerable subcutaneous edema involved both breasts and the skeletal musculature. Fluid just poured from the sectioned surfaces of the pale muscles including the diaphragm.

Grossly there were a few other significant findings. Although the liver was of normal size, its edge lay considerably below the rib margins, as a consequence of the low level (11th vertebra) of the diaphragm. The heart, which was of average size, had flabby musculature and severe arteriosclerotic narrowing of the right coronary artery ostium.

The microscopic findings were extremely interesting. Fragmentation of thickened coarse collagen bundles in the skin (Figure 1) were seen associated with a severe infiltration of lymphocytes and plasma cells. The skeletal muscle presented atrophy and loss of strial markings. The supporting stroma exhibited the same alterations observed in the dermis of the skin. There were hydropic and mucoid as well as inflammatory changes in the fat, and both degenerative

and inflammatory changes in the blood vessels were seen.

As you may already have inferred, we are dealing with the condition known as nonsuppurative myositis or dermatomyositis. In this conditon you see nicely striated muscle fibers, with a patchy distribution of muscle damage. Many fibers

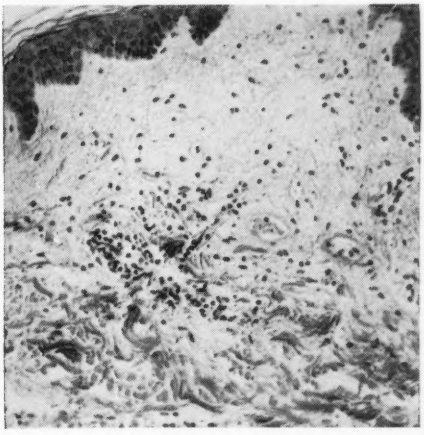


Figure 1
Skin showing edema and slight inflammatory infiltration of the dermis. The collagen fibers in the deeper layers of the dermis show foci of increased acidophilia and homogenization. X160

completely lose their normal appearance. Numerous multinucleated giant cells represent the limited and abortive extent to which skeletal muscle may regenerate.

In this case (Figure 2) the diaphragm was markedly affected and the dense inflammatory infiltration of its stroma can be recognized. In disseminated lupus with joint involvement there may be a similar but far less intense inflammation of the involved connective tissue. Diffuse muscular degeneration can also be seen. The process as shown here involves the pleural surface of the diaphragm (Figures 3 and 4) as well. With higher magnification we can observe that the infiltrating cells are almost exclusively lymphocytes, but there are occasional plasma cells. In this area we can note diffuse edema and fibrinoid degeneration. The changes, therefore, are acute as well as chronic.

In the lungs the significant microscopic findings were seen in the pleura. Both visceral and parietal layers were thickened and loculated accumulations of fluid were seen as little cavitations in the adhesions. Also observed were fibrinoid necrosis of collagen and a paucity of inflammatory reaction.

Although the heart was about normal in weight, it was soft and flabby. There was a marked increase of the connective tissue separating the muscle fibers (Figure 5) as well as inflammatory changes about some of the blood vessels. This

Figure 2
The pleural surface of the diaphragm is considerably thickened by fibrinous exudate and cellular (newly formed) fibrous tissue. Observe the inflammatory infiltrate which extends into the musculature. X45

interstitial type of myocarditis has been observed in other cases of dermatomyositis. With higher magnification no similarity to the perivascular Aschoff nodule of rheumatic myocarditis could be seen. Other abdominal organs showed lesser degrees of the serosal change observed in the diaphragm. A severe perisplenitis was found which presumably resulted from the proximity of the spleen and diaphragm.

Summarizing the disease, there was a widespread degenerative and inflammatory process involving skeletal muscle and connective tissue. Since clinically

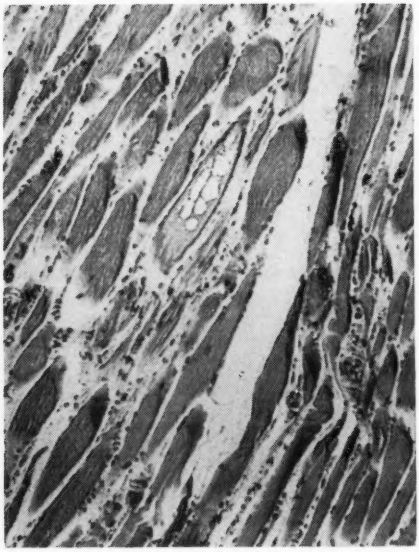


Figure 3
Hyaline and vacuolar degeneration of skeletal muscle. X110

as well as historically it was the skin in which the latter change was most evident, it has been designated dermatomyositis. In this case the severity of the lesion in the diaphragm seems to account very well for the puzzling respiratory distress observed clinically.

Dr. Joseph Freilich mentioned the various biopsies that were taken. There were negative findings in all investigations of the respiratory tree, the gastrointestinal tract, and the breasts. A muscle biopsy, however, might well have proved on diagnostic value.

In dermatomyositis, as in other degenerative and dystrophic lesions of muscle, there is a great increase of urinary creatine excretion. To differentiate dermatomyositis from disseminated lupus, it is helpful to recall that lupus is usually associated with moderate or even severe anemia, leukopenia, and a positive L-E test.

Interesting is the fact that there was severe edema, but the protein level and liver function tests were within normal limits. Liver disturbance played no part

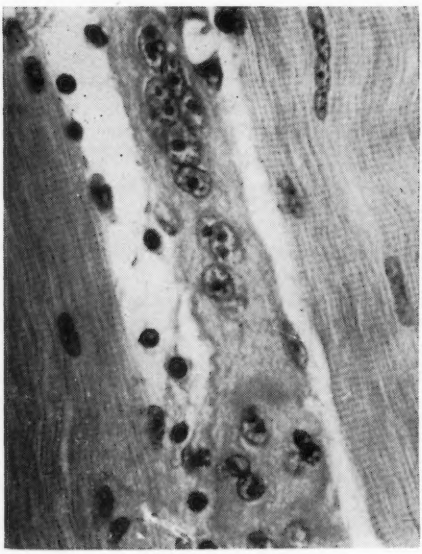


Figure 4
Multinucleated muscle giant cell. X600

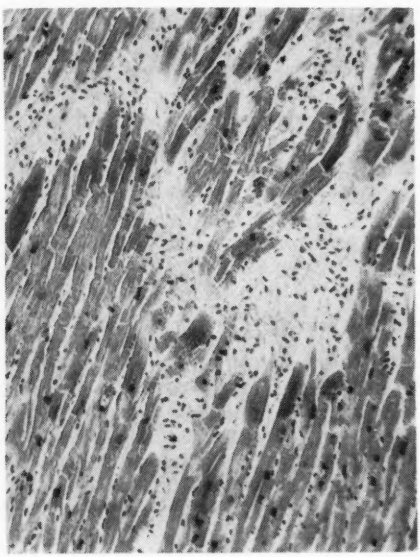


Figure 5
Interstitial myocarditis. X110

in the patient's edema. Since the autopsy disclosed no lesion of the parathyroids, the high values of phosphatase seem related to osteoporosis. Unfortunately, the literature on dermatomyositis does not make any reference to alkaline phosphatase.

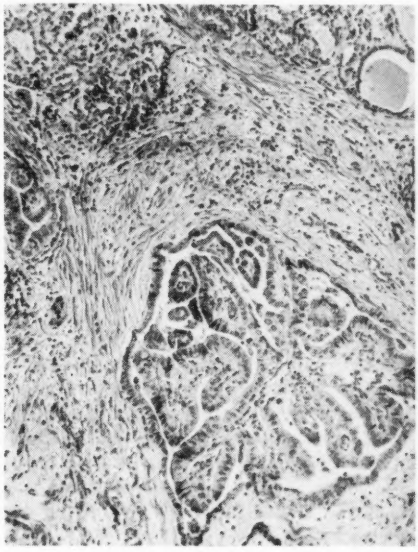


Figure 6
Minute papillary adenocarcinoma of thyroid.

One of the most interesting recent additions to our knowledge on dermatomyositis is that in an unusually large number of cases it is associated with cancer. Cancer of the ovary, breast, stomach, and gallbladder have been reported, and according to recent reports those who write about it claim the simultaneous occurrence of cancer and dermatomyostitis far exceed the possible statistical coincidence. In a recent review in 1951, eighteen such cases were gathered from the literature. As we reviewed this case on gross and microscopic examination we found no cancer. However, a section taken at random from what seemed like a small but normal thyroid disclosed a microscopic nodule of papillary neoplastic epithelial growth (Figure 6). Despite its size, there was a distinct invasion of lymphatic channels, indicating the lesion to be a papillary adenocarcinoma. Because of this chance finding, one wonders whether more careful pathologic studies might reveal an even higher incidence of malignant disease in dermatomyositis than has been reported. One writer even goes as far as to say that there may be an etiological relationship between this disease and cancer. There have been cases reported where the dermatomyositis improved after removal of a tumor, but recurred with its regrowth or metastasis. Such conclusions, of course, must be tempered with the recognition that dermatomyositis, especially in adults, improves spontaneously in about 50% of cases.

SCHOOL NOTES AND NEWS

FACULTY NEWS

Dean F. J. Mullin has been named to the Medical Advisory Board of the Multiple Sclerosis Foundation of America.

Dean Andrew H. Ryan was elected Director-at-Large of the Walter Reed Society and to the Board of Directors and Executive Committee of the Illinois Society for Medical Research.

Department of Anatomy

John James Chiakulas, Ph.D., has been appointed Instructor in Gross Anatomy.

Department of Biochemistry

Dr. A. Robert Goldfarb was elected Senior Member of the American Federation of Clinical Research.

Department of Dermatology and Syphilology

Drs. John A. Guerrieri, Eugene Lorant, and Arthur L. Shapiro have been promoted to Associate in Dermatology and Syphilology.

Drs. Irving Distelheim and Henry H. Morrison have been promoted to Instructor in Dermatology and Syphilology.

Department of Medicine

The following appointments have been announced by Dean F. J. Mullin.

Dr. Edwin R. Levin — Assistant Clinical Professor of Medicine.

Dr. Joseph A. Cohen — Associate in Medicine.

Drs. Anthony Bolino and Aaron Mincberg — Clinical Assistant in Medicine

Dr. Richard H. Kosterlitz — Full Time Instructor in Medicine.

Dr. George N. Lewis — Clinical Instructor in Medicine.

Drs. Irving Forman and Herbert Korol —Instructor in Medicine.

Dr. Abe L. Aaronson, Assistant Professor of Medicine, was elected President of the Chicago Society of Allergy, and appointed to the Medical Advisory Board of the Asthmatic Children's Aid Society.

Dr. Morris A. Kaplan, Assistant Professor of Medicine, was elected Member of the Board of Regents of the American College of Allergists, and to membership in the Illinois State Academy of Science and the American Association for the Advancement of Science. He has also been appointed to the Medical Advisory Commitee of the Asthmatic Children's Aid Society of Chicago, and was elected Chairman of the Section on Allergy of the Illinois State Medical Society.

Dr. Aldo A. Luisada, Associate Professor of Medicine, was appointed Chairman of the Section on Cardiovascular Physiology of the American College of Chest Physicians and also was appointed Consultant in Cardiology at the Veterans Administration Hospital, Hines, Illinois.

Department of Microbiology

Dr. Harold Elishewitz has been re-elected Chairman of the Commission on Parasitic Cultures of the Midwestern Conference of Parasitologists.

Department of Obstetrics and Gynecology

Dr. Lawrence LeVine has been appointed Clinical Assistant in Obstetrics and Gynecology.

Dr. Leonard P. Rapoport has been appointed Assistant in Obstetrics and Gynecology.

Department of Ophthalmology

Dr. Samuel I. Kaufman, Assistant Professor of Ophthalmology, was recently certified as Attending Ophthalmologist at the Cook County Hospital, where he is now assigned to the Glaucoma Clinic.

Department of Otolaryngology

Dr. Lloyd L. Matzkin was appointed Instructor in Otolaryngology.

Department of Pathology

Dr. Ira Gore has been appointed Associate Professor of Pathology.

Dr. Kurt Stern, Assistant Professor of Pathology, was elected a Member of the American Society of Human Genetics.

Department of Pediatrics

Dr. Lester J. Baranov has been appointed Assistant in Pediatrics, and Dr. Bernard Block has been appointed Clinical Assistant in Pediatrics.

Department of Physiology and Pharmacology

Dr. Ben B. Blivaiss was elected a member of the American Federation for Clinical Research and the Endocrine Society of America.

Department of Psychiatry

Drs. Myron Feld and Bernard Ratner have been appointed Associates in Psychiatry.

Dr. Samuel Burack has been appointed Clinical Assistant Professor of Psychiatry.

Dr. Theodore Dulin has been appointed Instructor in Psychiatry.

Dr. Rudolph Dreikurs, Professor of Psychiatry, was recently elected President of the American Society of Group Psychotherapy and Psychodrama, and Secretary of the American Society of Adlerian Psychiatry. He is also a Council member of Commission for Preservation of Medical Standards in Psychiatry.

Dr. Harry H. Garner, Professor of Psychiatry and Chairman of the Department, was appointed Chairman of the Sub-Committee on Psychiatry of the West Side Medical Center Veterans Administration Hospital of Chicago, and was appointed Psychiatric Consultant to the Veterans Administration Hospital, Hines, Illinois.

Dr. Francis O. Lamb, recently promoted to Assistant Clinical Professor of Psychiatry, was appointed Consultant to the Child Guidance Clinic at Benton Harbor-St. Joseph, Michigan, sponsored by the Mental Health Department of the State of Michigan.

Dr. Leroy P. Levitt, Instructor in Psychiatry, was appointed Consultant in Psychiatry to The Jewish Family and Community Service Association for Family Living.

Dr. Bernard Skorodin was promoted to Assistant Professor of Psychiatry.

Dr. Martha W. Piers was recently promoted to Assistant Clinical Professor of Psychiatric Social Work.

Dr. Walter A. Adams has been promoted to Assistant Clinical Professor of Psychiatry.

Department of Surgery

Dr. Isadore M. Isoe has been appointed Instructor in Surgery.

Dr. William Henry Newman has been appointed Clinical Assistant in Orthopedic Surgery.

Dr. Archibald D. McCoy has been appointed Associate in Neuro-Surgery.

Dr. Roger W. Poborsky has been appointed Associate in Orthopedic Surgery.

ALUMNI NEWS

Class of 1938

Dr. Paul Nierenberg has been appointed Second Year Resident at The New York Skin and Cancer Hospital of The Bellevue Medical Center, New York.

Class of 1940

Dr. A. Estin Comarr has been elected a Diplomate of the American Board of Urology. He has recently been appointed Clinical Instructor of Urology at The School of Medicine of the University of California at Los Angeles.

Class of 1944

Dr. Bernard K. Galston, on leave of absence from the Department of Anesthesiology, is now stationed at the 320th General Hospital, Landstuhl, Germany.

Dr. Irvin Seaman, having completed a Residency in Obstetrics and Gynecology at The Mount Sinai Hospital of Chicago, has announced the opening of his office for the practice of Obstetrics and Gynecology at 220 Miracle Mile, Coral Gables, Florida.

Congratulations to Dr. and Mrs. James Weishaus on the birth of their son, Kent Allan, July 23, 1953.

Class of 1946

Dr. Emanuel Chusid has recently been appointed Resident in Pediatrics at The Bronx Hospital, New York.

Dr. Arthur Dishman is presently serving in the United States Army Medical Corps and has been stationed at the United States Medical Hospital, Paris, France, for the past 18 months.

Dr. Normabelle Helman Shively (Mrs. John C. Shively) is to be congratulated on the birth of a daughter, Mary Susan, born August 1, 1953.

Class of 1947

Dr. Louis S. Cholden is now engaged in research with the United States Public Health Service at Bethesda, Maryland.

Congratulations to Dr. and Mrs. Norman Rosensweig on the birth of their daughter, Elizabeth Ann, October 21, 1953. Dr. Rosensweig is Senior Clinical Instructor in Psychiatry at the Neuro-Psychiatric Institute of The University of Michigan Medical School.

Class of 1948

Dr. Herbert Lipschutz, recently separated from the United States Army Medical Corps with the rank of Captain, is now engaged in private practice at the Lincoln Village Medical Center, 6199 N. Lincoln Avenue, Chicago, Illinois.

Dr. Stanley Reichman recently announced the opening of his office at 4 West 75th Street, New York City.

Congratulations to Lieutenant and Mrs. Louis Ruff on the birth of their son, Bradley, June 3, 1953.

Class of 1949

Dr. Harold E. Berson recently announced the opening of his office at 1620 Ditmas Avenue, Brooklyn, New York.

Dr. Edward Zucker, recently discharged from the United States Army Medical Corps after serving as a Captain in Korea, is presently a Resident in General Surgery at Saint Francis Hospital, Evanston, Illinois.

Class of 1950

Captain James R. Carey, having recently completed twenty months in the United States Army Medical Corps, has recently announced the opening of his office in the Lindauer Building, Lincoln, Illinois.

Dr. Herbert L. Fishbein is now a Resident in Roentgen, Radium, and Isotope Therapy at the John E. Jennings Hospital, Kings County Medical Center, Brooklyn, New York.

Dr. Leonard D. Grayson has recently been appointed Assistant Attending in Dermatology and Syphilology at The Long Island College Hospital and Visiting Clinical Assistant in Dermatology at The Kings County Hospital, Brooklyn, New York.

Dr. Abraham S. Ludwig, recently promoted to the rank of Captain in the Air Force Medical Corps, is now stationed at Atterbury Field, Columbus, Indiana.

Congratulations to Dr. and Mrs. Seymour R. Matanky on the birth of their daughter, Cindy Lee, May 20, 1953. Dr. Matanky is presently serving with the United States Medical Corps in Korea.

Class of 1951

Dr. Arthur S. Bresler has recently announced the opening of his office for the practice of General Medicine at 533 Riggs Road, N.E., Washington, D. C.

Congratulations to Dr. Walter A. Charles and the former Miss Elaine B. Ullman on the occasion of their marriage, June 20, 1953. Dr. Charles is now a Resident in Pediatrics at the State University of New York at Kings County Hospital, Brooklyn, New York.

Congratulations to Dr. and Mrs. Jesse Schessel on the birth of their son, David, May 23, 1953. Dr. Schessel is a Resident in Pediatrics at Brooklyn Jewish Hospital, Brooklyn, New York.

Congratulations to Dr. Jerrold J. Schwartz on the receipt of the Degree of Master of Industrial Health from Harvard University.

Class of 1952

Congratulations to Dr. and Mrs. Harold Dorin on the birth of their son, Paul, September 1, 1953. Dr. Dorin has recently announced the opening of his office for the practice of General Medicine at 1617 Cravens Avenue, Torrance, California.

The *QUARTERLY* would like to take this opportunity to congratulate the following members of the Class of 1952 on their appointments to the following Residencies:

Dr. Martin Bernstein—Jackson Memorial Hospital, Miami, Florida—Urology.

Dr. Robert Bragman—Madison General Hospital, Madison, Wisconsin—Anesthesiology.

Dr. Gilbert Douglas—Veterans Administration Hospital, Hines, Illinois—Surgery.

Dr. Arnold Grier—Mount Sinai Hospital, Miami Beach, Florida—Internal Medicine.

Dr. Jacob Ladenheim — Cook County Hospital, Chicago — Ophthalmology.

Dr. Sidney Schucter—Cleveland Clinic, Cleveland, Ohio—Internal Medicine.

STUDENT NEWS

Class of 1954

Congratulations to Martin Abrams and the former Miss Lynn Epstein, both of New York City, on the occasion of their marriage, June 22, 1953.

President John J. Sheinin has announced that Stanley Bauer was the winner of the Senior Scholarship for having attained the highest scholastic average in the Junior year.

Congratulations to Lionel Bernson of Paterson, New Jersey, and Miss Mitzi Campbell of Beverly Shores, Indiana, on the recent announcement of their engagement.

Leonard and Barbara Braunstein proudly announce the birth of their first child, Frederick M., on November 20, 1953.

Congratulations to Alfred Fader of Cleveland, Ohio, and Miss Delores Pitner of Berwyn, Illinois, on the announcement of their recent engagement.

Best wishes to Lawrence Feuerman of Waterbury, Connecticut, and Miss Mildred Schwartz of Chicago, Illinois, on the announcement of their engagement.

We wish to congratulate Sherman E. Goldberg and the former Miss Lynn Wodis of Galesburg, Illinois, on the announcement of their marriage, October 3, 1953.

Congratulations to Sanford Allen Kaplan of Brooklyn, New York, and Miss Maxine Schoenfeld, also of Brooklyn, on the announcement of their engagement.

Best wishes to Marvin Keller of the Bronx, New York, and Miss Shirley Eichel, of Chicago, on the recent announcement of their engagement.

We wish to congratulate James Keuer and Miss Jo Ann Schlegl, both of Chicago, on the announcement of their engagement.

Congratulations to Jules Michel of Oaklyn, New Jersey, and the former Miss Evelyn Katz, of Chicago, on the occasion of their marriage, September 27, 1953.

Congratulations to George and Beverly Paul on the occasion of the birth of their first daughter, Susan Helene, on October 15, 1953.

Melvin and Pearl Post proudly announce the birth of their first child, Robert Mark, on December 10, 1953.

Congratulations to Sheldon and Lila Schein on the birth of their first daughter, Linda Suzanne, on November 27, 1953.

Best wishes to Norman Shapiro of Merced, California, and the former Miss Phyllis Ehrenberg, of San Francisco, on the occasion of their marriage, September 27, 1953.

Class of 1955

Congratulations to Jack Gilman of Chester, Pennsylvania, and the former Miss Renee Bloemendaal, of The Netherlands, on the occasion of their marriage, November 14, 1953.

Best wishes to Philip Mozer of Denver, Colorado, and the former Miss Beverlee Levins, of Chicago, on the announcement of their marriage on August 30, 1953.

President John J. Sheinin has announced that Aaron Lou Southern was the winner of the Junior Scholarship for having attained the highest average in the Sophomore year.

We wish to congratulate Helmuth Stahlecker and the former Miss Vera

Plesko, both of Chicago, on the announcement of their marriage, July 11, 1953.

Congratulations to Lawrence Strenger and Miss Mildred B. Levine on the recent announcement of their engagement.

Class of 1956

Best wishes to Gerald Klebanoff and Miss Roberta Schneider on the recent announcement of their engagement.

ORGANIZATION NEWS

Student Council

The Annual Spring Dance sponsored by the Student Council will be held this year at the Conrad Hilton Hotel on Saturday evening, April 24. This is the third Annual Dance and promises to surpass the great successes of the preceding years. Entertainment will be provided by the Sophomore Class, whose talents hope to exceed the excellent performance given by last year's Sophomore Class. As in the past, the faculty is cordially invited to spend an evening of pleasure and relaxation with the entire student body.

Phi Lambda Kappa

As the present quarter draws to a close, we of Phi Lambda Kappa look back with pride upon the accomplishments of this quarter and continue our plans for the future.

On October 10, 1953, we held our first dance of the year at Highland Park. It was an informal affair that was open to members and non-members alike, as are most Phi Lambda Kappa affairs.

In conjunction with our brother chapter at the University of Illinois, we held our Annual Fall Dance at the Illini Union on November 14, 1953. Late in the evening we had the pleasure of viewing one of the all-time motion picture classics, "Lives of a Bengal Lancer," which was obtained from the Museum of Modern Art.

Future affairs for next quarter which are now being planned include a Pledge Dance and Induction Dinner, the latter to be held Sunday afternoon, January 31, 1954, at the Sheridan Plaza Hotel.

Phi Delta Epsilon

The Beta Tau Chapter of Phi Delta Epsilon began their functions this year with a Smoker for prospective pledges at the Illini Union on October 17, 1953, and had as guest speakers several faculty members and Alumni. The Annual Pledge Dance was held on November 14, 1953, at the Knickerbocker Hotel where a grand time was had by all.

The Fifth Annual John J. Sheinin Lectureship was held this year at the Kling Auditorium of the Mount Sinai Hospital of Chicago where Dr. Paul Aebersold, Director of Isotope Research at Oak Ridge, spoke on "The Progress in Diagnosis and Treatment of Diseases by Radioactive Isotopes."

Association of Internes and Medical Students

Dr. Peter Gaberman, Associate Professor of Medicine, presented a very enlightening and provocative talk sponsored by AIMS on November 25, 1953. His subject was "Medicine and Money," and in addition to discussing some of the financial aspects of medical practice, Dr. Gaberman analyzed the many forms of medical practice that are open to physicians in this country and abroad.

Student American Medical Association

The Student American Medical Association of The Chicago Medical School began a successful quarter with a very stimulating lecture by Dr. Philip Thorek on "Intestinal Obstruction." Dr. Thorek spoke before a capacity audience in Amphitheatre A.

As part of the educational program of SAMA a film program was presented, among which were films on "Glaucoma" and "Bronchoscopic Examination."

Plans are now being completed for the Annual Convention to be held at the Hotel Sherman, Chicago, on May 1, 2 and 3, 1954. All Student A.M.A. members are invited to attend. A free trip to New York via Capitol Airlines, and a weekend stop at the Waldorf-Astoria Hotel will be awarded one of the members attending the convention.

BOOK REVIEWS

TREATMENT OF MENTAL DISORDERS by Leo Alexander, M.D. Cloth. 507 pages. Philadelphia and London: W. B. Saunders Company, 1953. $10.00.

This is an extremely readable and informative text which will be of great value to the beginning psychiatrist or neurologist. The author emphasizes that psychic and physical aids to psychiatric treatment must be combined as one instrument of therapy. Each chapter is followed by an extensive list of references for the benefit of those who wish to read further on any particular topic. Principles and techniques of psychotherapy, electroshock and electrostimulation, drug therapy, and psychosurgery are discussed. Results and complications of psychotherapy and physical treatment are given a prominent place. The text is of interest to the medical student who plans a neuropsychiatry specialty. It covers the subject completely and authoritatively and is a "must" reference book for every medical school library.

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AN ATLAS OF SURGICAL EXPOSURES OF THE EXTREMITIES by Sam W. Banks, M.D. and Harold Laufman, M.D. Cloth. 391 pages with 552 illustrations. Philadelphia and London: W. B. Saunders Company, 1953. $15.00.

This is a truly comprehensive atlas which fills a long-standing need for such a book in the textbook armamentarium of the surgeon. No operative details are included, but only the actual exposure and its underlying anatomy. The exposures emphasize preservation of function. The drawings are remarkably clear and well-reproduced. They are the result of cadaver dissections and photography of each of the steps of the exposure. The photographs were then collated and important structures were labelled. These photographs served as the basis for rough drawings from which the final drawings in the text were made. Textual material has been kept at a minimum. The atlas is certainly a necessity for the surgical resident and the orthopedic surgeon and may also serve, as the authors put it, as a "refresher" for the experienced surgeon who operates on the extermities only occasionally.

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CURRENT THERAPY 1953. Edited by Howard F. Conn, M.D. with a Board of 12 Editorial Consultants. Cloth. 835 pages. Philadelphia and London: W. B. Saunders Company, 1953. $11.00.

Once again, *Current Therapy* presents an impressive list of consultants and contributors. As in the past, the material represents the actual therapeutic methods used by the authority who describes them. Diagnosis, unless it is an integral part of therapy is not discussed. The presentations are concise and to-the-point. Current methods, whether old or new, are included with the aim of making the vast amount of therapy readily available to the busy physician. This book has its greatest value for the general practitioner. Indeed, it is inconceivable that he can get along without it.

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PHYSICAL EXAMINATION OF THE SURGICAL PATIENT by J. Englebert Dunphy, M.D., F.A.C.S. and Thomas W. Botsford, M. D., F.A.C.S. Cloth. First Edition. 326 pages with 188 figures. Philadelphia and London: W. B. Saunders Company, 1953. $7.50.

Here is a fine text which systematically and thoroughly emphasizes the physical diagnostic aspects of the surgical patient. It is an excellent book for the student who is often in need of a guide to the examination of the surgical patient. The text includes discussions of the disease entities only briefly and practically and is a good supplement to the fuller texts of surgery. For the general practitioner it serves as a means of reviewing and systematizing his approach to the surgical patient. The book is divided into two large sections: the elective examination — which logically covers each system of the body; and the emergency examination — which covers the approach to the important and more common traumatic and emergent surgical conditions. The illustrations, except for the x-rays which are photographs, are drawn. This is advantageous in that the drawings are clear and easy to visualize. However, the text is an excellent one, covering its material thoroughly and serving a practical need for a well-organized approach to the examination of the surgical patient.

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BCG VACCINATION: STUDIES BY THE WORLD HEALTH ORGANIZATION TUBERCULOSIS RESEARCH OFFICE prepared under the direction of Lydia B. Edwards, M.D., Carroll E. Palmer, M.D., Ph.D., and Knut Magnus, cand. act. Cloth. First Edition. 307 pages with many tables and figures. New York: Columbia University Press, 1933. $3.00.

This monograph describes a piece of international research and study into the many aspects, disputes, and technical problems surrounding BCG vaccination. The study, which covered a period of three years, utilized various groups of school children as subjects. Such matters as the effects of temperature, duration of storage, exposure to light, dilution of the vaccine, and the various methods of producing the material to be used are all covered in extreme detail. The report serves as a valuable "source book" and reference work for anyone interested in BCG research. It also contributes many valuable findings, well-founded experimentally, which will help solve many of the important issues concerning BCG. It will serve all those who are interested in this highly controversial and interesting field with vital information and well-designed studies which supply facts and figures on which one may base a sound opinion on the matter. It is a fine example of the work being done by the World Health Organization.

FUNDAMENTALS OF PSYCHIATRY by Edward A. Strecker, M.D., Sc.D., Litt.D., F.A.C.P. Cloth. Fifth Edition. 250 pages with 21 illustrations. Philadelphia: J. B. Lippincott Company, 1952. $4.50.

This thorough, yet relatively brief, textbook of psychiatry is dedicated to, and written for, the student and practitioner "Who, wishing to be *complete* physicians, realize that man is unified and total in his functioning and that, therefore, human disease must be treated, not merely at the level of somatic pathology, but also in the area of emotional conflicts and their deceptive psychosomatic expressions." The approach is logical, beginning with the more general aspects and leading to the specific clinical entities one encounters. The discussions are clear and cover all aspects of an entity, such as etiologic factors, psychopathology, laboratory findings, symptoms, prognosis, differential diagnosis, and therapy. A glossary of important terms also adds to the value of the text. In general, the book stresses the problems which will confront the practitioner of any of the medical specialties or general fields and succeeds in orienting the medical man in relation to relatively "pure" psychiatric entities as well as psychosomatic medicine. It is highly recommended to all who seek a sounder knowledge of the patient as a whole.

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CLINICAL DIAGNOSIS BY LABORATORY METHODS by James Campbell Todd, Ph.B., M.D., Arthur Hawley Sanford, A.M., M.D., and Benjamin B. Wells, M.D., Ph.D. Cloth. Twelfth Edition. 998 pages with 946 illustrations, 197 in color, and 403 figures. Philadelphia and London: W. B. Saunders Company, 1953. $8.50.

After five years, and with the passing of the senior author, Drs. Sanford and Wells have brought this outstanding text up to date but have not performed any drastic changes in this revision. The format is essentially that of the eleventh edition, with notable alterations in the chapters on urine and blood and standardization of the nomenclature and methods in the fields of bacteriology and serology. This book needs no introduction and the thoroughness and easy readability of the material needs no description. Valuable references are placed at the end of each chapter and a useful appendix which includes such material as an index-outline of laboratory findings in important diseases and tables of various normal laboratory values add to the value of the text. It is an excellent text for a physician who desires to do the simpler laboratory procedures in his office and wishes a good background on which to interpret his findings. It also serves as a complete text, a "Working Manual of Clinical Pathology", for the student, describing all laboratory procedures and integrating them with clinical findings and pathophysiology.

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EXCERPTA MEDICA, SECTION XVI (CANCER, EXPERIMENTAL AND CLINICAL) by a Board of Editors, R. van Dam and W. van Westering, Editors. Amsterdam. Excerpta Medica, N.V. Vol. 1, No. 1. July 1953. $10.00 a year.

Long an outstanding abstracting journal, Excerpta Medica has added a new section on Cancer. The new section, like the existing fifteen sections, will be published monthly and will contain 700-800 pages of informative abstracts a year including a monthly index of authors and a classified subject and authors' index in completion of each yearly volume. The first issue contains a mass of material abstracted from journals published all over the world. It is presented in an easy to read and concise manner.

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WATER, ELECTROLYTE, AND ACID-BASE BALANCE by Harry F. Weisberg, M.D. 245 pp. 10 figures and 29 tables. Baltimore. The Williams and Wilkins Company, 1953. $5.00.

Anyone who has been fortunate enough to sit in on one of Dr. Weisberg's lectures will recognize that his terse and illuminating presentation has been carried over into his text. It is literally filled with "pearls" but, on the other hand, is not a book to read casually. The material and its method of discussion make it necessary reading for anyone desiring a thorough and up-to-date treatment of this subject, often an enigma to the average medical student. The information contained in the section on the normal physiology of water, electrolyte, and acid-base balance would be useful to the preclinical student in conjunction with the course in Physology and, of course, subsequently. The chapters devoted to pathologic physiology are an indispensable adjuvant to judicious and effective therapy. An extensive list of references is provided for those interested in original articles on the subject.

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ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE, VOLUME XXXI: PSYCHIATRIC TREATMENT, edited by S. Bernard Wortis, M.D., Morris Herman, M.D., and Clarence C. Hare, M.D. Cloth. 451 pages with 62 tables and 49 figures. Baltimore: Williams and Wilkins Company, 1953. $9.00.

This volume is the thirty-first in a series of research publications pertaining to the field of psychiatry and its material is drawn from the proceedings of the Association for December 14 and 15, 1951, at which time psychiatric treatment was covered. Many of the most outstanding men in the field report herein on group and individual psychotherapy along with biological, electrical, and pharmacological treatments, and neurosurgery. It hardly seems necessary to point out the value of this book. It serves as a thorough and critical survey of the relative merits of the various means with which the psychiatric patient is treated today. Each paper is written by an active worker evaluating and describing a mode of therapy he has followed himself. Such a volume as this is clearly designed for the psychiatrist in particular as a magnificent summary of current methods, but it will also serve the advanced student with budding interest in the field as an excellent source of the most recent and stimulating aspects of the field of psychiatric therapy.

ABSTRACTS SECTION

ATLAS, DONALD H. *(Asst. Prof. of Med.)* and H. KAMENEAR *(Asst. in Med.)*. Rupture of Echinococcus Cysts into the Bile Ducts Simulating Stones in the Common Duct. Amer. Jour. Med., *13* (3): 384-386, 1952.

Two cases are reported of rupture of echinococcus cysts into the bile ducts simulating stones in the common duct. The syndrome is characterized by the sudden onset of pain, followed by urticaria and a shock-like state. Both cases were immigrants. Eosinophilia was present in both patients. Obstructive jaundice subsequently developed. The diagnosis was established at surgery in one patient and enabled the authors to recognize the condition prior to surgery in the second case. The authors note that in Australia, where echinococcus infestation is common, sudden onset of biliary colic and jaundice is more frequently caused by echinococcus cysts than biliary stones.

Since publication of this article, it has come to our attention that infestations of the echinococcus may occasionally occur in native Americans in the southern part of the United States, who have never been outside the continental limits.

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ESSENBERG, J. M. *(Professor of Microscopic Anatomy)*. Chronic poisoning of the endocrine glands of female albino mice by cigarette smoke, Western Journal of Ob. and Gyn., V. 60, pp. 635-638, Dec., 1952.

Albino mice of strain "A" variety were exposed to the smoke of twelve cigarettes daily except Sunday for fourteen months. The following effects were noted:

1. Major pathology in the thyroid gland and suprarenal cortex. The damage consisted of cellular atrophy and hyaline degeneration.

2. Less marked pathology noted in the pancreas consisted of a decrease in the number of islands of Langerhans and atrophy of pancreatic acini.

3. No pathology could be demonstrated by histologic means in the pituitary and parathyroid glands. The effect on reproduction and the growth rate indicates functional damage to the anterior pituitary.

4. Nicotine is considered to be the major damaging agent.

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ESSENBERG, J. M. *(Professor of Microscopic Anatomy)*. Cigarette smoke and the Incidence of Primary Neoplasm of the Lung in the albino mouse, Science, Vol. 116, No. 3021, pp. 561-562.

The exposure of albino mice to longer durations and larger quantities of tobacco smoke than in a previous experiment, administered by a specially designed automatic smoking machine, was correlated to the incidence of primary neoplasm of the lung in these animals. Cigarettes were used as the source of the tobacco smoke.

Strain "A" mice, with a hereditary tendency to lung tumors, were used in a preliminary experiment. After fourteen months, twenty-one of twenty-five mice examined were found to have definite primary neoplasms of the lung, as determined by microscopic study of both lungs, serially sectioned, and stained with hematoxylin and eosin.

In a second experiment, using controls, the tumors in the exposed mice exceeded those for the control mice by 31.9%, a statistically significant figure.

It is concluded that cigarette smoke consists of several carcinogenic chemicals, among which are tars, arsenic, and nicotine itself.

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FOA, PIERO P., S. BERGER, L. SANTAMARIA, J. A. SMITH and H. R. WEINSTEIN. *(Dept. of Physiol. and Pharm.)* Extraction of the Hyperglycemic-Glycogenolytic Factor (HGF) of the Pancreas with Liquid Ammonia. Science *117*:82. Jan. 23, 1953.

Liquid ammonia is known to be an excellent solvent for many proteins, including insulin, which dissolve in it with a minimum of deterioration and little or no loss of physiological activity. Because of the close chemical similarities between insulin and HGF, an attempt was made to extract the latter by means of liquid ammonia. The HGF with chemical and physiological properties similar to those of the HGF described by others could be extracted from lyophilized whole pancreas or stomach powder by means of anhydrous liquid ammonia. The active principle can be partially purified by fractional precipitation in 80% alcohol. Semi-purified powder thus obtained produces a marked hyperglycemia in the dog when injected in doses of 1 mg./kg. body weight.

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KOENIG, HAROLD and STAHLECKER, H. *(Dept. of Anat.)* Use of Perchloric Acid for Nucleic Acid Histochemistry in Mammalian Nerve and Liver Cells. Proc. Soc. Exp. Biol. and Med., 79:159-163, 1952.

PNA was completely extracted from fixed sections of liver by 18 hours of treatment with 10% perchloric acid at 4° C. No significant quantity of DNA was removed by such treatment even after 93 hours of incubation. The above treatment is inadequate to extract PNA completely from nerve cells. However, with formalin-fixed nerve tissue, 12 hours incubation in 10% perchloric acid at 20° C and 15 minutes at 37° C was found to effect complete extraction of PNA with no loss of DNA. At higher temperatures of extraction, the margin of safety between complete removal of PNA and incipient extraction of DNA was much smaller. Prolonged hardening of nervous tissue in 10% formalin rendered PNA resistant to extraction by perchloric acid. Perchloric acid extraction of fixed sections of nervous tissue removed insignificant quantities of nerve cell protein. Cell structure was unaltered by this extraction procedure. This extraction procedure did not alter the E2537A of two tissues without PNA, skeletal muscle, and ribonuclease-treated nerve cells. It was suggested

that this procedure could be employed to provide tissue "blanks" in ultraviolet microabsorption spectroscopy for PNA in tissue sections.

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NIERMAN, MURRAY M. *(Alumnus 1943)* Treatment of cystic acne vulgaris with a cutaneous vasoconstrictor (Kutapressin). The Jour. of the Indiana State Med. Assn. *45*(6):497-502. June, 1952.

Twenty-two cases of cystic acne vulgaris who had been refractory to the conventional types of therapy showed marked improvement when given injections of Kutapressin, a preparation containing a cutaneous vasoconstricting factor present in the liver. The best results were obtained on a regimen of 1 cc. injections of Kutapressin given thrice weekly. In some cases, the acneiform lesions disappeared completely, and in others they were greatly reduced in number, size, and severity. The scars and pits regressed and the surface became more smooth and more normal appearing. Improvement was manifest after a few injections. No untoward effects were observed. Since all these patients had been sufficiently treated by the conventional methods without satisfactory results, they served as their own controls.

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SIEGEL, IRVING *(Assoc. Prof. of Ob. and Gyne.)* and M. GOLDIN. The sterility of stored placental blood, Obstetrics and Gynecology, Vol. 1, No. 4, April, 1953.

The sterility of placental blood was determined by culturing for anaerobic and aerobic organisms. The placental blood was collected by a closed system similar to that used in blood banks. Of seventy specimens, 98.7% were sterile. The authors think that placental blood could be a source of utilizable blood for transfusion or fractionation.

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SPIESMAN, MANUEL G. *(Assoc. Prof. of Proct.)*, B. CHAPMAN *(Assoc. in Surg.)*, and L. MALOW *(Inst. in Surg.)*. Rectosigmoidal Polyps, Amer. J. of Proctology, V. 2, No. 4.

A resume of twenty-five years of experience in the treatment of rectosigmoidal polyps is presented in a simple and concise manner. The incidence of polyps in cancer detection centers as well as in private proctologic practice is given. The conclusions drawn after noting the above figures indicate that a sigmoidoscopic examination should be performed on all patients over 35 years of age.

Classification of polyps is suggested for use as follows:

1. Benign Polyps
   a. Resting Polyps
   b. Actively Proliferating Polyps
2. Polyp with Carcinoma in Situ
3. Polyp with Infiltrating Carcinoma

The pathological criteria for this classification is presented in detail with photomicrographs which demonstrate the different types.

The tendency for malignant degeneration in benign polyps is quite high as evidenced by various figures quoted.

The treatment of polyps is broken down into those above or below the peritoneal reflection and whether sessile or pendunculated. The different types of treatment such as dessication, snare, Frankfeld cup, or surgery is discussed and their advantages and disadvantages given.

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STEINER, KARL and GRAYSON, L. *(Alumnus, 1950)*. Sodium Para-Aminobenzoate ("PABA") in the treatment of Dermatoses, J. of Investigative Dermatology, Vol. 19, No. 6, December, 1952.

Twenty patients with a variety of inflammatory skin diseases received up to sixteen grams of sodium para-aminobenzoate (PABA) daily by mouth for periods ranging from two weeks to several months. Two of the twenty patients showed good and lasting improvement. Four other cases responded initially but relapsed after a few weeks.

Intracutaneous reactions to known allergens were not changed by PABA.

There were positive Thorne test responses subsequent to the intake of two to four grams of PABA. These positive Thorne tests, though unrelated to clinical responses, indicated a definite effect of PABA.

PABA might be tried in otherwise therapy-resistant inflammatory skin diseases, and its effect by the parental route and in lower doses could be investigated.

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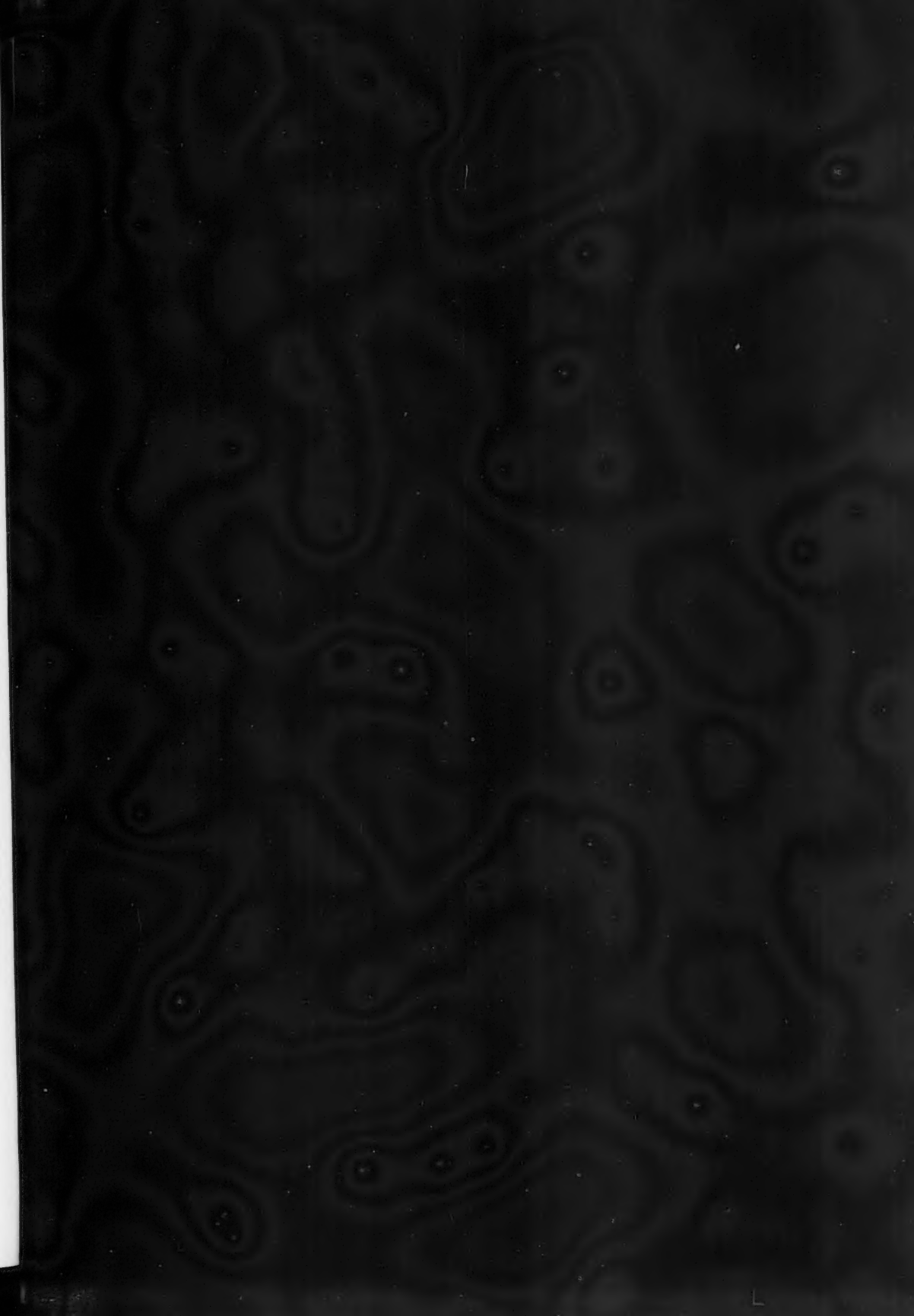
STINE, LEONARD A. *(Assoc. in Med.)* and ANDREW C. IVY. The effect of psychoanalysis on the course of peptic ulcer: A preliminary report. Gastroenterology. *21* (2), June, 1952.

In reviewing the medical literature on psychoanalysis and peptic ulcer, only one follow-up case report was found of the results of the treatment on the course of the disease. Since the efficacy of treatment can be judged only in terms of the results achieved, and in view of the growing interest in the psychiatric aspects of the treatment of ulcer patients, the authors have undertaken a long term follow-up study of ulcer patients who have been psychoanalyzed in order to try to evaluate the influence of this type of therapy on the frequency and severity of ulcer recurrences.

A preliminary report is presented discussing the method used, including its advantages and disadvantages as well as its limitations, some of the theoretical aspects of the problem, a review of the relevant literature, and a small number of suitable cases. The purpose of this report is to help in finding new case material.

Because of the very small number of cases so far available for study, no conclusions can be reached as yet. Of seven suitable cases, two have had no recurrences eighteen and fifteen months following the completion of the analyses. Three have had recurrences, but are definitely improved, and two are considered unimproved. All of these cases were considered by the therapist to have improved markedly with respect to their personality problems following psychoanalysis.



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